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THE TREATMENT OF SYPHILIS WITH SALVARSAN

THE TREATMENT OF SYPHILIS WITH SALVARSAN

BY

Sanitätsrat Dr. WILHELM WECHSELMANN, of Berlin

Medical Director of the Skin and Venereal Disease Section, Rudolph Virchow Hospital, Berlin

WITH AN INTRODUCTION BY

Professor Dr. PAUL EHRLICH, of Frankfurt-on-Main

Director of the Royal Institute for Experimental Therapeutics, Frankfurt.

ONLY AUTHORIZED TRANSLATION

BY

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Revised Edition, with an Appendix bringing this Literature up to date, by ABR. L. WOLBARST, M.D., of New York

WITH 19 TEXTUAL FIGURES AND 10 COLOURED ILLUSTRATIONS

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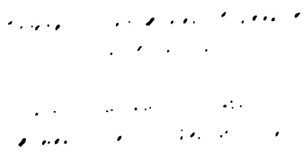

PREFACE TO THE SECOND EDITION

When this work was translated, salvarsan had not yet been presented to the medical profession. A comparatively few clinicians were entrusted with sample quantities, but none had the clinical opportunity that was given to Wechselmann by virtue of his extensive service in the Rudolf Virchow Hospital.

Wechselmann's observations made at that time stand unchanged to-day, with but few exceptions of minor importance.

The time that has elapsed, has confirmed Wechselmann's original opinion that salvarsan exerts an influence on syphilis of a most extraordinary character, differing in many respects from that exerted by mercury.

While mercury may be regarded, in some quarters, as a specific for syphilis, it must be admitted that its action is slow in comparison with that of salvarsan, and that it is often ineffective in cases that respond most beautifully to the new remedy. We should bear in mind that any comparison between the efficacy of mercury and salvarsan, is based on one or possibly two or rarely three doses of salvarsan, as compared with a course of persistent mercury medication lasting for weeks and months. Possibly the near future has a solution to the hidden properties of this new remedy, as applied to syphilis. New methods of administration, more careful technique, a better understanding of its contraindications and means of overcoming them,—all of these must eventually increase many fold the value and potency of salvarsan in the treatment of syphilis.

Some of this added knowledge has been selected from the literature and personal experience, and added to this edition in the new chapter following the translation.

In response also to a growing demand for detailed information, chapters have been added on the spirochetes and the serum reaction of Wassermann.

The former is practically a translation from Klopstock-Kowarsky's "Praktikum," with slight modifications suggested by the writer's personal experience. Bosanquet's "Spirochetes" has also been freely consulted.

The chapter on the Wassermann reaction is also taken mainly from Klopstock Kowarsky, with suggestions from Noguchi and other writers. It is hoped that both of these chapters will be of value to the reader.

The writer, in closing, desires to express his thanks to Dr. N. Kruskal, of New York, for valuable assistance and kindly suggestions.

ABR. L. WOLBARST.

TRANSLATOR'S PREFACE

This work of Doctor Wechselmann seems to be particularly opportune at this moment, now that Ehrlich's wonderful product, salvarsan, has been placed before the general medical public and also in view of the widespread interest with which it has been received. Doctor Wechselmann enjoys the distinction of having been invited by Professor Ehrlich in February 1910, to use the new remedy in his extensive service at the Rudolf Virchow Hospital in Berlin.

More than fourteen hundred cases treated with salvarsan have been studied by the author up to the date of going to press, and I deem it a great pleasure as well as a rare privilege to be able to present the results of these epoch-making studies to the English-speaking medical public. I believe the readers of this volume will concur in my opinion that it combines all the essential features of a large clinical experience, scientific methods of investigation and broad, conservative judgment.

In translating this work, a studied attempt has been made to adhere as far as possible, to the original text, even as to paragraphing and at times in spite of minor discrepancies as to dates, size of dosage, etc. The drug itself has been designated in the original by more than half a dozen names, including "606," "Ehrlich-Hata," "Arsenobenzol," "Ehrlich's remedy," "Dioxydiamidoarsenobenzol" and so forth. For the sake of uniformity however, an exception has been made in this sole instance and but one name has been used for the preparation in the translation. At first it was thought wise to use the abbreviated name "arsenobenzol," but on later inquiry, Professor Ehrlich informed me that he preferred that the name "salvarsan" be used. This name has been adopted throughout the work excepting in Professor Ehrlich's Foreword, in which the original has been permitted to remain unchanged.

The literature of the subject is essentially and necessarily German. Wechselmann's "Review of the Literature" therefore consists almost entirely of German titles, which are beyond the reach of most English-speaking readers. I have therefore thought it would be well to incorporate a list of the writings of American and British observers, who have either had some personal experience with the new remedy, or have abstracted and collated the writings of foreign contributors. It is hoped that this bibliography will prove of value to the students of this work. American readers will also observe that certain words in the text have been spelled in accord with the custom prevailing in Great Britain. This is in compliance with the request of the English publishers.

Wherever it has been possible, weights and measures have been transposed from the metric to the English system, and the Fahrenheit equivalent has been substituted for the Centigrade temperature. It is believed that these changes will be of advantage to readers who are accustomed to dealing with English measures and the Fahrenheit thermometer.

I desire to take this opportunity to express my deep gratitude to Professor Ehrlich and Doctor Wechselmann for the many courtesies, personal and professional, which they extended to me during my brief stay in Germany, and particularly for their manifestation of good will in expressing the wish that I translate this volume into English. My sincere thanks are also extended to Mrs. A. L. Wolbarst, who has rendered invaluable service in the translation and to Doctor Paul Rosenheim for many helpful suggestions.

ABR. L. WOLBARST

105 East Nineteenth Street, New York

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FOREWORD

Believing that a critical review of the collective experiences and of the values found in testing salvarsan would fill a much-felt want, the literature upon the subject having grown to enormous proportions, it gives me pleasure to comply with a request to write a few prefatory remarks introducing the present monograph.

That its author is thoroughly conversant with his subject is made evident by the fact that he stands among those who have assisted in erecting, upon the firm foundation laid by Alt and Schreiber, the structure which to-day may serve as a guide-post for all of us who are administering and judging the new preparation in human therapy. With untiring zeal and penetrating comprehension, Wechselmann undertook the labourious and responsible task of testing the new method of treatment on the large clinical material at his disposal; and we owe to his power of critical observation an important collection of data, by which authoritative rules have been established for guidance in the further therapeutic employment of salvarsan.

If I am to limit myself only to the most important of Wechselmann's personal observations, which are so clearly stated in the following pages, I desire to state that he was the first to point out the excellent effect of salvarsan, particularly in those cases of malignant syphilis where the former methods of treatment often failed after years of medication. Wechselmann has also shown that in just such cases, it is possible without any particular risk, to repeat the injection, and thereby attack the cause of the disease a second time, when we have not been able to master it at one stroke.

Furthermore, Wechselmann's explanation of the causation of local

recurrence after treatment with salvarsan, appears to me to be of particular importance. He assumes that it is due to spirochetal foci, which cannot be attacked by the remedy on account of an imperfect vascular supply. I believe that this opinion will also readily explain the particularly disagreeable surprise caused by the recurrences recently observed in nerve-trunks. Similar symptoms have hitherto been observed only in patients where the disease was in the early period of the secondary stage. It is thus quite clear that in this stage of the disease, in which the entire organism is saturated with spirochetes, individual foci may escape sterilization, especially when they are localized in parts either without blood-vessels or poorly vascularized; subsequently they may flare up, as a localized recurrence, unless they are overcome by a reinjection, which hits the mark like a sure shot, so to speak (Fangschuss), permitting of no escape.

According to the more recent experiences, Wechselmann's explanation seems to me very plausible. There is no ground for declaring that a toxic irritation caused by the preparation is responsible for this phenomenon, for numerous experiences have already demonstrated the fact that salvarsan has no neurotropic effect. In this respect, too, we have to thank Wechselmann for having satisfactorily shown that even syphilitic affections of the optic nerve and retinal atrophies may be treated without causing injury; this could hardly be done if salvarsan really had a toxic effect on the nerve-terminations.

Lastly, I should also like to mention, in this connection, the modification of the method of administering the remedy introduced by Wechselmann. Undoubtedly, the adoption of Wechselmann's painless method of neutral suspension made it possible to test the remedy more freely than heretofore, inasmuch as the method of injection formerly employed was often accompanied by severe pain. In spite of the acknowledged merits of this new method, however, the manifold experiences we possess to-day will justify me in pointing out its shortcomings.

Apart from the imperfect absorption of the unevenly distributed particles of the suspension, these consist in the appearance of secondary phenomena, which take the form of long-continuing infiltrations, and occasionally, of necrosis. Although such consequences may not be considered

of too great importance, it seems that the *ictus therapeuticus* (therapeutic attack) of the subcutaneous and intramuscular injection is frequently not what it ought to be, especially as regards the permanency of the effect. Therefore under certain conditions, the energetic *ictus therapeuticus* of the intravenous application, which has been made certain as the result of many observations, is to be preferred to other methods, being especially indicated in the early symptoms of syphilis. Moreover, any anxiety as to a repetition of the injection, which is justified in the deposit treatment, need not be considered in this connection. Nevertheless, in spite of the change, I believe that for the reason already mentioned, Wechselmann's modification, which at the time of its introduction removed a very great obstacle to the practical testing of the remedy, is a highly meritorious achievement of the author, and equally as important as the facts discovered by him through scientific deduction and practical experience.

Thus the author has been able to utilize his skill, and in a large measure to draw on his own fountain of knowledge in the preparation of this book. The clear, illuminating presentation of the subject, its beautiful general make-up, and especially the excellent reproduction of the illustrations and tables, through the firm of Dr. Selle & Co., deserve the most laudatory comment, as they impart a brilliant vestment to the rich contents of the work. Therefore I am inclined to believe that it will readily find its readers, even without especial recommendation.

P. EHRLICH.

FRANKFORT-ON-THE-MAIN,

INTRODUCTION

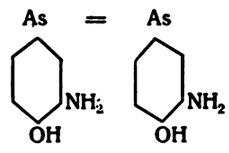
Among the great investigators who first and most thoroughly studied the curative power of the organism against the attack of parasites, and who recognized the processes concerned therein, Ehrlich undoubtedly ranks foremost. It is principally due to his ingenious and profound researches that to-day many infectious diseases can be treated "specifically," in a modern sense, i.e., directly or indirectly, with bacterial products. Ehrlich's clear insight also enabled him to recognize the fact that in many diseases the salutary reaction of the organism encounters serious obstacles in the very nature of the parasites. In these instances, the attempt has repeatedly been made empirically to cause the disappearance of the parasites by the use of chemical agents; as, for instance, the quinine treatment of malaria, the mercury and iodine treatment of syphilis, and the atoxyl treatment of sleeping sickness. Especially in the case of syphilis, it has long been known that arsenic also sometimes produces a certain effect; but it amounted to very little, and besides, was very unreliable (see Rosenthal, *Berliner klin. Wochenschrift*, 1908, No. 3). Consequently arsenic has heretofore never played any great part in the therapy of syphilis; and only now and then it has been used with some measure of success in cases where treatment by mercury failed to produce the desired result. Uhlenhuth in experimenting with atoxyl on animals, observed that it exerted a curative and prophylactic influence on spirillosis in chickens, and therefore suggested its use in syphilis. However, though the treatment of syphilis with organic preparations, especially atoxyl, has resulted successfully in some cases, it was soon generally abandoned on account of its dangerous effects, particularly upon the optic nerve; the same is true of arsacetin. It may also be stated, according to Zieler, that the combined use of atoxyl and mercury, which Uhlenhuth and his co-workers tested on animals with excellent result, and which was also used in human pathology with apparently good result, has not been shown to be sufficiently established.

Ehrlich's Chemo-therapy.—From the very beginning, Ehrlich adopted a different plan. Pharmacology heretofore only taught us the toxicity of

the respective remedies, but left us altogether in the dark in regard to the principal point, namely, the means by which the remedy was enabled to cure a given disease. Ehrlich on the contrary, created an actual experimental therapy, studying biologically the curative processes in experimentally induced diseases. He thus demonstrated the condition termed by him "tropism," i.e., the specific relationship and storage of curative agents, in the organs as well as in the parasites. Basing his procedure upon his exhaustive studies, he prepared synthetically and tested such remedies as would, with a minimum of poisonous effect on the organism (minimum organotropism), produce the maximum poisonous effect on the parasites (maximum parasitotropism). He first employed atoxyl, the constitution of which, with the assistance of Bertheim, he demonstrated to be the sodium salt of a p. aminophenyl acid, a very stable and at the same time a strongly reacting substance. By transforming and attacking the amido group, Ehrlich succeeded in obtaining an infinite variety of compounds, all of which contained the radical of an organically fixed arsenic acid. These compounds could be rendered non-poisonous, or made more poisonous at will; and their effect upon the animal organisms, as well as upon parasites, could thus be readily investigated. By this method it was demonstrated that trypanosomes can assimilate the organic derivates of arsenic acid only when the arsenic radical is present in the form of three valens, while they are indifferent in the presence of five valens. Especially when the arsenic-resisting (arsenfast) strains were studied, it was found that the protoplasm of parasites contains a number of specific chemo-receptors, which cause anchoring of the drug, and consequently the parasiticidal effect.

During the course of years, out of hundreds of substances experimented with on animals, only a few were found to be available, particularly arsacetin, arsenophenylglycin and salvarsan, the last prepared at the Speyerhaus by Dr. Bertheim according to the following formula:

Salvarsan.
Hata's Experiments.



At the request of Ehrlich, Hata studied this substance on animals, with these results (*Verhandlungen des deutschen Kongresses für innere Medizin*, Wiesbaden, 1910, *Chemotherapie der Spirillosen*):

"Of this substance, mice will tolerate 1 c.c. of a $\frac{1}{100}$ dilution for every

20 gm. of body weight. One c.c. of a $\frac{1}{800}$ dilution is still capable of sterilizing an infected mouse weighing 20 gm.; the effect of still weaker dilutions, e.g., 1:1,000, is uncertain. The *dosis tolerata* of this substance for rats is 0.2 gm. per kilo, the *dosis curativa* being 0.06 gm. per kilo.

	Dosis Tolerata	Dosis Curativa	$\frac{C}{T}$
Mouse	1/300 gm. per 20 gm.	1/800 gm. per 20 gm.	$\frac{1}{2.7}$
Rat	0.2 gm. per kilo.	0.06 gm. per kilo.	$\frac{1}{3.3}$

"Curative effects may be produced even with smaller doses, but only when repeatedly administered.

Tabulated Results of Experiments with Salvarsan in Mice

Dose	Permanently Cured After		
	One Application	Two Applications	Three Applications
1:600	100%	—	—
1:700	100%	—	—
1:800	100%	—	—
1:1,000	75%	100%	100%
1:1,500	18%	75%	100%
1:2,000	16%	66%	100%
1:3,000	—	—	33%

"It is not advisable to give the injection more than three times; nor is the effect of more than three injections any greater than that of two or three.

"This remedy also possesses a prophylactive effect against recurrent fever in mice, and particularly in rats, although the protection is of but brief duration.

"The disagreeable by-effects in the nervous system, i.e., tremor, dancing, and especially amaurosis, which are so readily produced by atoxyl, arsacetin, etc., have never been observed in animals treated with salvarsan. The alkaline solution, however, when subcutaneously injected, produces a more or less distinct infiltration at the site of injection, apparently causing considerable pain and possibly necrosis, if the amount injected is too great.

"As compared with recurrent fever in mice and rats, the cure of chicken spirillosis is effected far more easily. Uhlenhuth succeeded in curing this disease by administering atoxyl and atoxylate of mercury. Chicken spirillosis can also be cured without much difficulty with arsacetin and arsenophenylglycin, both of which, like atoxyl and atoxylate of mercury, are almost entirely ineffective in recurrent fever in mice. The facility with which chicken spirillosis can thus be cured, makes it a suitable medium for testing a remedy as to its effect on spirilla in general, and especially to compare it with the effectiveness of various other remedies. I submit the following table to show the comparative efficiency of the various remedies and their toxic properties:

Results of Treatment for Chicken Spirillosis

Infection Intramuscular	Treatment Two Days After Infection, Also Intramuscular		
Remedy	Dosis Tolerata Per Kilo	Dosis Curativa Per Kilo	$\frac{C}{T}$
Atoxyl	0.06 gm.	0.03 gm.	1/2
Arsacetin	0.1 gm.	0.03 gm.	1/3
Arsenophenylglycin	0.4 gm.	0.12 gm.	1/3.3
Arsanilate of Mercury	0.1 gm.	0.04 gm.	1/2.5
Salvarsan	0.2 gm.	0.0035 gm.	1/58

"This comparison clearly shows that the results with the first four remedies are far less satisfactory than that with the salvarsan, in which the ratio $\frac{C}{T}$ is actually ideal.

"In the prophylactic experiments with salvarsan, a very interesting fact was revealed, which I would briefly mention in this connection. I injected 0.07 gm. per kilo intramuscularly into chickens, and found that the animals after thirty days still remained completely immune to infection. However, thirty-five days after the treatment, the infection appeared; but it was very slight, and only after fifty days could a protective effect be no longer determined.

"On the other hand, if the remedy is administered intravenously, the protective effect barely lasts four days; and six days after the injection, the animal reacts quite normally towards the infection.

"The reason of the extremely long duration of the protective effect in the case of the intramuscular injection was clearly demonstrated at once

by the fact that at the site of injection, a large deposit of the remedy was discovered. The remedy causes coagulation of the muscle, and remains firmly combined with it for a long time. Gradually the substance is absorbed from the coagulated mass and transferred to the blood; but even fifty days after the injection the presence of the deposit in the muscle can still be distinctly determined.

"As we have already seen, the parasites are destroyed by a minimum amount of the substance; the small quantities absorbed from the deposit are evidently sufficient to stop their growth.

"Although the explanation of this fact is quite simple, it is undoubtedly of great importance in the practical application of the remedy. The intramuscular application is to be preferred to the intravenous in the prophylaxis of chicken spirillosis, because the protective effect of the former method is far more certain and lasting than that of the latter.

"It is still uncertain whether, in deposits of this kind, unexpected injury may not follow, or sudden intoxication may occur, or the pain may be of long duration. For this reason I am of the opinion that in human therapy, the intravenous application, where the remedy is completely eliminated from the body within a few days, is to be preferred to the intramuscular injection.

"Finally, we also made therapeutic experiments in syphilis. We used rabbits, in which it is well known three forms of syphilis may be artificially produced, namely, syphilitic keratitis, syphilitic chancre of the scrotum, which was first studied by Truffi—and syphilitic orchitis, recently described by Uhlenhuth. Keratitis in rabbits is a very unreliable medium for experimental work, inasmuch as the clinical symptoms sometimes spontaneously disappear, only to reappear later. Therefore this disease is not suitable for therapeutic experiment. Syphilitic orchitis is quite suitable for maintaining the strain, because it offers a pure culture; but chemotherapeutic studies cannot be very well pursued in this regard, because the swelling of the testicle alternately increases and decreases of its own accord. These two forms of syphilis in rabbits are especially unsuitable for repeated examinations for the spirochetes, and this is of great importance in chemotherapeutic experiments. In the case of chancre, however, this is simply and readily affected by pricking the edge of the infiltration with a needle, and making pressure. A fresh specimen is taken from the drops of serosanguinous liquid then appearing, and this is studied under the microscope with the dark field illumination.

"The method of inoculating the scrotum is as follows: At some point

of the scrotum of a full-grown rabbit, a small incision is made in the skin, and a pocket is formed into which some of the inoculating material is inserted as deeply as possible. After some ten to fourteen days, a small white or slightly reddish infiltration appears at the point of inoculation, growing slowly until it attains the size of a bean approximately. After four or five weeks, the skin at this point gradually becomes necrotic and a crust forms. The margin of the ulcer thus developed is of cartilaginous consistency, and projects above the surrounding healthy skin. When the moist crust is removed, slight bleeding sets in from the foul necrotic base, the latter being sometimes so much depressed as to cause a distinct elevation of the marginal infiltration. Thus the picture presented greatly resembles the primary chancre in man. The entire induration gradually increases in size and thickness, occasionally measuring an inch in diameter and three-fourths of an inch in thickness. This condition lasts for several months. Only such animals were selected for the experiments in which the pathologic condition was unmistakable and stationary.

"The rabbit comfortably tolerates an intravenous injection of 0.1 gm. of salvarsan per 1,000 gm. of body-weight. When the chancre is fairly well developed on the scrotum, showing innumerable spirochetes, one injection of a sufficient dose of the remedy is administered intravenously. On the very next day, the spirilla have completely disappeared from the chancre, and a few days later the crust has become dry and the induration is very soft, disappearing completely after about seven to ten days, at which time the crust falls off entirely. Within two to three weeks the large chancre has been reduced to a small scar. Of course, rapidity of the complete destruction of the spirochetes depends upon the size of the dose administered, but also upon the size and especially the thickness of the induration and the number of the spirochetes. If the dose is too small, or the chancre extremely thick, the spirilla will take two or three days to disappear. For complete healing, two to three weeks are generally required; this naturally depends upon the size of the chancre and the presence or absence of suppuration, that is, mixed infection. Should any other complication arise, for example pneumonia, the process of healing may be considerably retarded. For this reason therefore, the disappearance of the spirochetes is a far more certain criterion of the effect of a remedy than the time required for complete healing of the chancre.

"In my therapeutic experiments with salvarsan, I obtained the following results:

Results of Treating Syphilitic Rabbits with Salvarsan. One Intravenous Injection.

Dose Per Kilo	Relation to Dosis Tolerata	Spirochetes Disappeared Within	Complete Cure (if without complication)
0.04 =	1/2.5	24 hours	2 to 3 weeks
0.03 =	1/3	24 "	2 to 3 "
0.02 =	1/5	24 "	2 to 3 "
0.015 =	1/7	24 "	2 to 3 "
0.01 =	1/10	2 days	2 to 3 "
0.0075 =	1/14	2 to 3 days	2 to 3 "
0.005 =	1/20	2 to 3 " (with one exception)	3 to 4 "
0.004 =	1/25	Still present after 30 days	Not cured
0.003 =	1/30		

"According to these figures, a dose of 0.015 to 0.01 gm. per kilo is required for immediate sterilization. This is one-seventh to one-tenth of the *dosis tolerata*. But rabbits may be ultimately cured with smaller doses, even with 0.005 gm. per kilo, or one-twentieth of the *dosis tolerata*. The dose of 0.3 gm. thus far administered to man, actually corresponds to this small dose given to rabbits. Further observation will determine whether or not it is sufficient to prevent subsequent recurrence in man, or whether larger doses must eventually be administered."

Thus we see that here we have a remedy by which the three types of spirochetes are absolutely destroyed without injury to the organism of the host, i.e., a remedy capable of readily curing animals infected by spirochetes. Whether the remedy will come up to all the requirements of general practice can only be determined by additional research, which must be carefully pursued in the laboratory and at the bedside.

The Application of Chemical Preparations, Derived from Animal Experimentation, to Human Pathology.—Ehrlich has thoroughly explained the difficulties of applying these chemo-therapeutic substances, obtained by animal experimentation, to human pathology. The principal difficulties are these:

1. In contrast with the experiments in animals, it is evidently impossible to administer the maximum well-tolerated dose to man, or to determine the same; it is therefore necessary to experiment carefully and

patiently to ascertain the effective dose, beginning with the smallest doses and gradually increasing them.

2. Frequently we encounter primary sensitiveness and acquired hypersensitiveness in man. More than one-half of all medicinal substances, even when administered in small doses, will produce by-effects not pertaining to the disease; and when administering new and peculiar chemicals, this tendency will always have to be taken into consideration. It is well to remember that these chemicals, owing to their active character, may give rise to serious phenomena occasionally.

3. The greatest obstacle is to be found in the existence of primary sensitiveness and acquired hypersensitiveness (idiosyncracy); for this reason, the new remedies must be experimented with only when it is possible to observe the patient carefully and continuously.

When these remedies are administered, patients should be kept in bed, their diet carefully regulated, and the pulse and temperature constantly kept under observation. Furthermore, in the presence of any complications, such as inflammation or degeneration of the liver or kidneys, which may exert an unfavourable influence on elimination, the remedy should not be administered; while in the aged, and in persons suffering from advanced disease, it should be prohibited absolutely. Before administering the new remedy, any specific injury to a given organ, the *locus minoris resistentiæ*, should be ascertained, to determine if such organ will be particularly endangered by the use of the chemical. When the patient is suffering from any ocular disturbance, atoxyl and arsacetin must not be used. It is still more important if it is possible, to ascertain by cautious preliminary tests, the degree of susceptibility of the patient.

Two methods must be taken into consideration in chemo-therapeutic treatment:

1. **Consecutive Treatment.**—The method of continuous treatment by consecutive stages. This consists of the injection of small, harmless doses, which temporarily cause the disappearance of the parasites, but are not sufficiently powerful to prevent their recurrence. A complete cure is aimed at by repeating the injections at frequent intervals, e.g., every fourteen days.

2. **Therapia Magna Sterilisans.**—The method of *Therapia magna sterilisans*. In this method an attempt is made to destroy the parasites within one or two days by a single treatment. This method is more difficult than the former, and may be more dangerous. However, in the experiments on animals, brilliant results have been achieved, the

degree of success depending on the species of the animal experimented upon.

At the conclusion of the experiments on animals, Ehrlich had the preparation tested by Professor Alt, at Uchtpringe, in regard to its toxic properties in man. On March 15, 1910, this investigator communicated to the *Münchener medizinische Wochenschrift* the fact that for a year and a half he had been experimenting with intramuscular injections of arsenophenylglycin, using single doses of 0.8 to 1.0 gm.; and that in one hundred and twenty-one paralytics with a positive Wassermann reaction, the reaction had completely disappeared in twenty cases. Since September 1909, Alt and Hoppe had been experimenting with salvarsan. After a number of experiments made on dogs in reference to its toxicity, two physicians permitted themselves to be injected with the preparation, and they experienced nothing but pain and swelling at the point of injection, and no ill effects whatever. Then Alt continued his work on paralytics, injecting the remedy deeply into the gluteal muscles, according to the method hereinafter described. The injection was very painful; neither infiltration nor abscess was observed, but there was a temporary rise in temperature to 102° F. Occasionally there was also irregular heart action, headache and vomiting, but at no time albumin or sugar in the urine. Generally the patients gained weight. In eighteen paralytics, in whom 0.3 gm. had been administered, the Wassermann reaction disappeared entirely in two cases, in two others there was a marked decrease, and in three the decrease was appreciable. Hoppe and Fischer found that the elimination of salvarsan still continued on the tenth day, in contrast with the rapid elimination in the case of atoxyl, arsacetin, and arsenophenylglycin. Leucocytosis was also observed.

After Alt had found that 0.3 gm. was a safe and efficient dose, he requested Dr. Schreiber, of Magdeburg, to use the preparation in cases of recent syphilis; and the latter was able to report astonishing results in the treatment of twenty-seven patients. Initial lesions decreased in size within a few days, and the infiltration also generally disappeared; the maculo-papular eruption, moist and ulcerating in character, rapidly became pale or dry, leaving only some flat pigment spots. Ulcerations of the labia became smooth and healed within a few days. Extensive condylomata of the anus and vagina soon became pale and smooth; and in several very severe cases, disappeared within four weeks, without leaving a trace. Also in one case, a very large and obstinate tertiary ulcer of the thigh became almost entirely cicatrized within less than three weeks. The most rapid

results were observed in the otherwise very obstinate cases of specific angina with slimy false membrane. In four out of the twenty-seven patients, the Wassermann reaction disappeared.

Hoppe and Schreiber then reported to the German Congress for Internal Medicine, similar results in one hundred cases observed by them. In twenty-five patients with positive Wassermann reaction, it became negative in twenty-three cases within forty days or more, i.e., in 92 per cent.

In March, 1910, Iversen read a paper before the Society of Russian Physicians, in St. Petersburg, on the action of salvarsan in cases of recurrent fever (published in the *Münchener medizinische Wochenschrift*, April 12, 1910). Iversen injected small doses, 0.05 gm. at first subcutaneously, and subsequently intramuscularly, and later increased the dose to 0.3 and 0.4 gm., as the smaller doses were not effective. It appeared that within four to ten hours all spirochetes disappeared from the blood, and the temperature fell to normal. In 92 per cent. of the fifty-two cases treated there was no recurrence. In the case of a hysterical and alcoholic luetic woman, who had been treated with mercury, the spirochetes disappeared within fourteen hours; however, on the fourth day, the temperature rose to 102° F., and the case gave the impression of a secondary infection, with double broncho-pneumonia. He says: "The erythema, which was not hemorrhagic at first, might have been taken for that of scarlet fever; but the subsequent developments, namely, acute nephritis, edema of the upper part of the body, enlargement of the liver, and hemorrhage of the skin, followed by death on the eighth day after the injection, made the case evidently one of idiosyncrasy. Marked arteriosclerosis, myocarditis, fatty liver, and other gross changes in the vital organs having been found at the post-mortem examination, it seems quite certain that here we encountered a number of unfortunate complications, which led to the fatal result." Iversen then began to administer the intravenous injection of salvarsan; he accurately described its technique, the details of which will be mentioned later on.

PERSONAL EXPERIENCES IN FOURTEEN HUNDRED CASES

On February 18, 1910, while these experiments were being made, Privy Councillor Ehrlich also entrusted me with the remedy to be used in further experiments on a more extensive scale. The remedy was to be administered in doses of at least 0.3 gm., in patients with syphilis, otherwise healthy and not heretofore treated with mercury, as only in this way could success in the form of a *sterilisatio magna* be expected; the repetition of small doses, and the employment of the remedy in cases already treated to some extent, was to be avoided, owing to the possibility of hypersensitiveness (idiosyncrasy) being present in the patients. However, as I was unable to estimate in advance the dangers which might be incurred by such treatment, I proposed that experiments be made at first in children suffering with hereditary syphilis, and affected with pemphigus. According to all experience, the internal organs in these children are replete with spirochetes to such an extent that death is inevitable, with or without mercurial treatment. I began these experiments early in March. I soon ascertained that a very miserable child, rapidly nearing death with Little's disease, tolerated 0.03 gm. very well, administered intramuscularly. When it died fourteen days later, the organs did not show any changes, macroscopic or microscopic, that might have been attributed to the arsenic. In all the children most gravely affected with syphilitic pemphigus, the symptoms receded rapidly. In a few cases, however, there was a rise in temperature, severe anemia, and in two cases a peculiar opisthotonus appeared; and while some of the children recovered, three cases resulted fatally. But here too, the post-mortem examination showed no signs of arsenic poisoning. Nevertheless, it seems to be possible that through the rapid dissolution of the enormous quantities of spirochetes following the administration of salvarsan, such a large amount of endotoxins is liberated that severe and fatal injury may be caused to the feeble organism of the infant. This seems to be indicated by the fact that we no longer had any deaths later on,

when we injected only 0.015 to 0.02 gm., repeating the dose after eight days; the result as to the disappearance of the clinical symptoms was very satisfactory.

The first cases were the following:

CASE 1.—Waldemar V. D., five months old. Mother syphilitic, poorly nourished. Generalized tuberculo-papular syphilide, partly ulcerated. Coryza. Spirochetes + + +. On March 15th, salvarsan 0.033 gm. March 16th, marked decrease of the syphilides, which completely disappeared in a few days. The temperature rose to 104° F., falling to normal during the following days, again rising to 104° F., and then falling again. Congestion of the lower lobes of the lungs; opisthotonus; pupils reacting to light; spasms of the upper and lower extremities.

Post-mortem examination: Pneumonia; multiple gummata in the cardiac muscle; specific osteochondritis; internal organs normal.

CASE 2.—Erna J., born March 15, 1910. Face, body, and extremities covered with a dense papulo-squamous, partly pemphigoid, universal syphilide (see Plate X); coryza. On April 4th, salvarsan, 0.015 gm. Wassermann reaction + + + +; April 14th, exanthem not improved. April 15th, salvarsan 0.015 gm. repeated; after both injections, the temperature rose somewhat. April 20th, exanthem disappearing; April 24th, completely healed. So far, the improvement has remained constant, without any recurrence. Weight of body increased from 6 pounds 6 ounces to 6 pounds 13 ounces, although a wet-nurse's milk could be given but a short time. Wassermann reaction became negative. But as it returned to + + +, on June 27th, 0.03 gm. was injected again, and the Wassermann reaction once more became negative. The child has since remained healthy.

CASE 3.—Max S., born January 28, 1910, of syphilitic mother. Maculo-papular, universal syphilide; pemphigus of soles of feet; coryza. On March 17th, salvarsan, 0.02 gm. No increase of temperature. March 18th, exanthem disappearing; coryza improving. March 29th, entirely recovered. Wassermann reaction + + +, and remained so. The child lived, without recurrence, until June 11th, and then died from malnutrition, as it was impossible to procure a wet-nurse.

CASE 4.—Käthe M., born February 7, 1910. Coryza; generalized papulo-squamous syphilide; pemphigus. Inunctions were not well borne. Many new pustules appeared. On March 30th, salvarsan, 0.02 gm. March 31st, temperature 104° F. in the evening, next day falling to normal. Exanthem disappearing. Weight of body increased from 4 pounds 13 ounces on March 30th, to 4 pounds 15 ounces on April 2d. April 4th, death. Post-mortem examination showed death due to marasmus only. Internal organs normal.

CASE 5.—Wilhelm F., born January 27, 1910. Mother recent luetic; treated

here from September, 1909, to January, 1910. Poorly nourished child, having yellowish-grey complexion; coryza; rhagades in corners of mouth; universal papular syphilide. Spirochetes +. On March 29th, salvarsan, 0.023 gm. March 31st, symptoms much better. April 1st, death. Temperature had risen since March 30th to 102.2° F.

Autopsy: Internal organs pale, otherwise normal; epiphyses also normal; liver filled with numerous miliary gummata.

In view of the fatalities and cases of blindness observed following the use of arsenic preparations, our misgivings were such that the introduction of a new derivative of arsenic could only be made possible if it could be shown that the remedy would either cure syphilis or that it produced better results than the treatment with mercury. The former was impossible with a disease running a course so distinctly chronic, and interrupted by recurrences separated from each other by decades—a disease in which it is still impossible to determine whether or not a cure has resulted. For this reason I resolved to take the alternative by applying the new method of treatment to cases that did not respond favourably to mercury.

CASE.—Willy D. came under my observation in the village of Obdach, in 1906, when he was eighteen years old, suffering from malignant lues, which did not respond to injections of calomel and the Zittmann treatment. When the Virchow Hospital opened, he was assigned to Professor Buschke's service, from whose case history I learned the following: In October 1906, rosette-shaped syphilides still remained upon his body, the pharynx showed an ulcerating necrosis, there was thickening of the bones, and particularly on the lower surface of the glans, there were eight deep ulcers the size of a pea. He was given inunctions, sajodine, injections of calomel, arsenic (Pil. Asiatic and injections), steam and sulphur baths, and potassium iodide. Beginning in February 1907, the fever reached 102.2° F., for weeks, and to facilitate swallowing it became necessary to spray the throat with anästhesine. In March two courses of inunctions were given. On April 28, 1907, the efflorescences had partly healed and partly granulated; the lesions on the head were still unchanged; the uvula was destroyed. Zittmann treatment and iodipine. April 28th to May 7th, bichloride injections. May 23d, three atoxyl injections of 0.2 gm. each were given, and then discontinued. This was followed by two courses of inunctions. He was then discharged because he refused to submit to further treatment. His throat had healed, leaving large scars, and the skin syphilides had disappeared, excepting a few efflorescences the size of a quarter, on the buttocks. On June 12th, he went to the Charité with a renewed outbreak of skin lesions. Ten atoxyl injections were given, followed by six injections of calomel. In November, he went to the Lichtenberg Sanitarium where he was given thirty-two inunctions, iodide of potassium and sajo-

dine. In April, an ulcer reappeared upon the penis, which slowly increased in size. On May 20, 1908, he was discharged and admitted to the Virchow Hospital (Professor Buschke). Injections of arsenic and calomel, iodide of caseine, iodide of potassium and inunctions. August 31, 1908, improved and discharged at his own request. November to December 1908, again at the Charité; treated with calomel. February to June 1909, at Lichtenberg; inunctions. In August 1909, again at the Virchow Hospital (Professor Buschke). October to December 1909, again at Lichtenberg; inunctions and calomel. January to March 1910, treated by Dr. Max Joseph, with inunctions and potassium iodide. April 2, 1910, admitted to my service. The patient's condition was very pitiful, with ulcerations in the throat and a bluish-red area about five inches in diameter on the inner side of the thigh, partly ulcerated and partly cicatrized. On the scalp, he presented a similar necrosed area covered with extensive ulcerations of an unctuous, serpiginous character. There was marked thickening of the bones. On the penis a deeply fissured, greasy ulceration covered the entire surface of the glans and the shaft, extending deep down to the fascia, and leaving only a number of isolated skin-covered areas the size of a lentil. The patient stated that since the onset of the disease in 1906, the penis had been entirely covered with skin only for a few days.

On April 13, 1910, salvarsan, 0.25 gm., was administered; the temperature rose to 101° F., the patient otherwise feeling well, but suffering from severe pain; morphine injection. April 14th, 99° to 101°; morphine injection; general condition good. April 15th, 99.5°; in the evening, 102.5°; morphine injection; general condition good. April 16th, 99.5° to 101.5°. Beginning with April 17th, the temperature began to decrease and the pain disappeared; healing progressed rapidly. April 20th, the scalp ulcer and the lesion on the thigh had almost entirely healed; the ulcerations on the penis had become cleaner and decreased in size. May 9th, all the ulcerations had healed and the patient need no longer remain in the hospital. May 20th, the scar on the corona of the penis was eroded, as the patient had evidently neglected himself entirely.

The patient recovered in a surprising manner. Weight of body, April 6th, [illegible] pounds; April 16th, 110 pounds; April 23d, 106.7 pounds; April 30th, 110 pounds. May 7th, 112.9 pounds.

As to the further progress of the case, the following may be noted:

The [illegible] scars remained well and firm, the scar on the penis broke [illegible] three weeks and at the same time, the lower end of the radius [illegible] previously diseased, commenced to swell, causing much pain. [illegible] the first right incisor tooth, a very small ulcer formed simultaneously. After a second injection of 0.5 gm. of the neutral suspension, [illegible] set in at once, the bone rapidly became painless and

returned to its normal diameter, while the penis was covered with healthy granulations and new epithelium.

As the penile wound refused to heal entirely owing to the great skin defect, I considered the advisability of resorting to a plastic operation; but as that did not promise much success, the scar being too thin and extensive, I again injected 0.5 gm. of the neutral suspension, on August 8th, whereupon all the lesions healed completely. No injurious effects upon the optic nerve, which might have been caused by these three injections, were observed, although the patient had previously gone through several courses of atoxyl. At present, the patient is able to work and seems to be permanently cured. The negative Wassermann reaction, which appeared in the primary stage and continued negative for a long time after the first injection, became strongly positive two months thereafter and then became gradually weaker after the second injection. The patient is at his work again.

The following report gives additional proof of the remarkable efficiency of the new preparation, as compared with other known remedies:

CASE.—Flora S., a working-woman, aged twenty-five, was infected with lues in July 1905, and submitted to several courses of inunctions and injections at the Charité. For years she could not retain her feces and being in a most miserable condition, she was admitted to my service on May 5, 1909. She presented numerous ulcers, 2 cm. deep, foul-smelling, and extending in a wide curve from the posterior commissure up toward the nates, each about 15 cm. in length, and composed of several smaller ulcerating masses. Those areas in which healing had partly occurred were indicated by atrophic scars on the borders of which serpiginous ulcers were situated. The rectum was densely infiltrated and presented two strictures, of a calibre that barely permitted the introduction of a finger, the strictures having many deep ulcerations. Wassermann reaction + + +, weight 99 pounds. Five injections of calomel were given, but were stopped on account of diarrhea; at the same time iodide of potassium was administered. From May 12th, inunctions; incontinence somewhat improved; weight of body, 88 pounds. Locally, Roentgen ray for the ulcers. On July 3d, patient was discharged at her own request, but little improved. Readmitted July 7, 1909. Treatment with potassium iodide continued and ulcers treated locally, as mercury did not agree with the patient. On May 4, 1910, the patient was in a condition somewhat worse than that shown in the cast (see Plates VI and VII); she received 0.3 gm. salvarsan; and in a few days, the ulcers began to heal and assume a cleaner appearance. On May 18th, the ulcers had completely healed, with the exception of a few small ones on the right side, which showed signs of continued improvement. At the same time, the condition of the rectum had greatly improved; rectoscopic examination showed only a small, flat erosion at the site of the stricture. The general condition improved greatly, though the

weight of the body remained stationary, at 88 pounds. The rectum healed completely. But as the small skin erosions did not yield to local treatment with iodoform, calomel and the internal administration of iodine, the patient was again given 0.45 gm. salvarsan on July 12th; an immediate improvement followed and complete recovery occurred within four weeks. While under observation previously, the patient had constantly given a negative Wassermann reaction. It remained negative from the date of the first injection of 0.3 gm. on May 4th until June 17th, or more than six weeks; but on July 5th, there was a change to a positive reaction (+ + +). On July 28th, the reaction was again negative, having previously shown a continuous series, representing every degree of strength. Repeated investigations made since then have always shown a negative reaction.

As a result of these and similar observations, the superiority of the new remedy over those hitherto known was fully demonstrated and I therefore felt justified in assuming the risk that naturally attached to any new remedy. It is well known that our present treatment with mercury, especially the insoluble salts, salicylate of mercury, calomel and above all, the oil of cinereum (grey oil), is not without its dangers. Medical literature reveals a large number of grave and even fatal cases of poisoning, that could not possibly have been foreseen and which occurred in spite of the best treatment (compare Lasserre: "Le passiv des injections mercurielles," in the *Annales de Dermatologie et de Syphilographie*, 1908).

On May 20, 1910, I demonstrated the great success of the new remedy to the Freie Vereinigung für Mikrobiologie, showing the results in forty cases. I repeated the demonstration at the Rudolf Virchow Hospital on June 7th, and on June 14th before the Freie Chirurgenvereinigung. This report was published in the *Dermatologische Zeitschrift*, Vol. XVII, Part 7.[1] On June 22, 1910, I reported to the Berliner Medizinische Gesellschaft, the results in eighty cases thus treated, presenting numerous patients, casts and photographs, showing the condition before and after

[1] Compare my publications: "Chemotherapy der Syphilis," Zentralblatt für Bakteriologie, 47. Bd., Beiheft, Referate 1910 (Discussion by Uhlenhuth, Hoffmann, Ehrlich); also, Berliner klin. Wochenschrift, 1910, No. 27: "Über die Behandlung der Syphilis mit Dioxydiamidoarsenobenzol;" Deutsche medizinische Wochenschrift, No. 32, "Beobachtungen an 503 mit Dioxyamidoarsenobenzol behandelten Krankheitsfällen"; also No. 37, "Über Reinjektionen mit Dioxydiamidoarsenobenzol"; and in No. 41, Transactions of the "Königsberger Naturforscher-Versammlung." Also my assistants, Dr. Lange, "Zur Kenntnis der Wassermannschen Reaktion, insbesondere bei mit Ehrlichs 606 behandelten Luesfällen," Berliner klinische Wochenschrift, No. 36; and Dr. Sieskind, "Zusammenfassender Bericht über 375 mit dem Ehrlich-Hataschen Präparat behandelte Fälle," Münchener medizinische Wochenschrift, No. 39.

treatment. I thereby proved that even the most skeptical could no longer doubt that the new remedy acts upon the symptoms of syphilis in all of its infectious forms, with a rapidity and thoroughness not even approximately exhibited by any other known remedy. However, I laid particular stress upon the fact that the questions as to recurrence, and above all, as to whether the remedy can possibly cure syphilis at one single stroke, could only be solved by continued observations. Moreover, the observations made at that time have been confirmed since then on all sides, and we can now consider the extraordinary effect of Ehrlich's salvarsan to be as follows:

Primary erosive chancres are frequently epidermized within forty-eight hours. Specific phimoses recede after the injection without any operative treatment whatever. However, healing is much less rapid in those cases of typical sclerosis consisting of a thick infiltrate of plasma cells and new connective-tissue cells, in which access of the remedy to the spirochetes is difficult or altogether prevented. For some time in our clinic, we have adopted the policy of destroying initial scleroses as far as possible, either by means of the Holländer hot-air apparatus, or by completely excising them. In this way we eliminate a large amount of spirochetic material, and what remains of it succumbs more readily to the action of the remedy. This policy seems to be the more justified, inasmuch as Hoffmann has been able to determine the presence of spirochetes in the scars of initial lesions, years after the primary infection. It might also be advisable, following Hallopeau's suggestion, to inject small doses of the remedy subcutaneously into the tissues adjacent to the primary lesion simultaneously with the ordinary injection. This might be recommended whenever the primary lesion comes under our observation very early and the enlargement of the inguinal glands is not yet very pronounced. Primary affections of the lip disappear with a startling rapidity and maxillary buboes also recede quite speedily. Gangrenous forms of primary lesions, based on a mixed infection of spirochetes and Rona's bacilli, heal very well after an injection of salvarsan, when the gangrenous tissue has been shed (see Plate I). Frequently enough, the opportunity has been offered in the case of mixed infection, to observe that after the disappearance of the typical scleroses, chancroidal ulcers remain, which of course, are not influenced by arsenic.

As an example, I would like to quote the following cases, which were also under observation for some time:

CASE 1.—Bertha M., aged twenty-one. Patient feeble; unctuous, hard chancre of left labium majoris, the size of a quarter; severe indurative edema. Right apex

of lung, dulness and râles. On May 26th, 0.456 gm. salvarsan; May 31st, primary lesion cleaner, edema almost entirely disappeared; June 6th, the entire erosion clean, except a few areas half the size of a dime. Weight of body on May 25th, 91.3 pounds; June 4th, 92.5 pounds; June 14th, 94.6 pounds; everything well. July 20th, entirely without symptoms. May 26th, Wassermann reaction + + +; June 2d, + + + +; June 10th, + + + +; July 20th, negative.

CASE 2.—C., aged twenty-five. Extensive primary lesion of the lower lip. Enormous maxillary bubo, the size of a man's fist. Universal papular syphilide. On April 23d, 0.3 gm. salvarsan; April 30th, primary affection and glands reduced to one-half their former size; May 18th, completely healed, except for a few slight pigment areas on the thigh. May 7th, weight of body, 153 pounds; on May 14th, 157.3 pounds.

CASE 3.—W., aged twenty-two. Enormous primary affection of the lower lip, the size of a dollar, greatly disintegrated; submaxillary glands as large as an apple. Inunctions were moderately successful. On May 21st, 0.4 gm. salvarsan. June 2d, the lesion was flat and reduced to the size of a dime. Glands very small and partly suppurated. June 8th, chancre almost healed; weight, 113.3 pounds. June 15th, completely healed. In August, no symptoms.

In the majority of instances, secondary symptoms do not appear after the disappearance of the primary lesion. In some cases nevertheless, an eruption has appeared. These two cases are especially illustrative:

A young colleague had two typical scleroses in the coronary sulcus, adjacent to the frenum, since July 15th. On August 13th, he received 0.5 gm. salvarsan. On the following day his temperature rose to 102.2° F. It fell to normal on the second day, coincidently with the appearance of a generalized papular syphilide. The chancre and likewise the syphilide healed rapidly in a few days. On October 21st, he was perfectly well; the primary lesion was no longer to be seen and the indolent inguinal glands had entirely disappeared. Wassermann reaction, August 13th, negative; on October 21st, negative.

I made a similar observation in a case of primary chancre of the upper lip; in this case eight days after the injection, though the primary lesion had healed, a roseola manifested itself and disappeared spontaneously within a few days.

The usual patches on the mucous membrane rapidly disappear, frequently within twenty-four hours, and for this reason they may be considered a valuable means of testing the effect of the remedy. Still more remarkably, the disagreeable lesions of the mouth and pharynx also disappear as by witchcraft, though they have been in existence for years. This healing process takes place even when the patients are inveterate smokers. The following case may serve as an illustration:

K., aged fifty-five. Infected one and a half years ago; twenty injections of mercury oxycyanide. In June 1909, patches in the mouth and ulcerations on the tongue; a course of inunctions administered at Nenndorf. In January 1910, ditto; in April and May 1910, protoiodide pills and potassium iodide. The tongue was covered with numerous patches and ulcerations; they never disappeared, gave the patient much pain and compelled him to give up smoking. He was prevented from taking anything but soft food and was hardly able to speak, his tongue being swollen and speech very painful. On August 17th, injection of 0.5 gm. salvarsan. On the very same day, the patient was able to speak without hesitation and on the following day he ate buttered bread without any difficulty; within about eight days thereafter, a complete cure was effected.

Broad condylomata of the genitals are dried and epidermized in a few days, a result of inestimable importance in regard to the question of infectiousness. For several days they remain elevated above the surface of the skin level then collapse and disappear.

In the same way the macular syphilides of the skin usually recede rapidly, sometimes within a few hours (see Plate XIII). One is apt to be deceived however, on account of the changing blood content of the skin; for sometimes when it becomes chilled, a few faded spots may remain for a number of days. Papular syphilides too, generally disappear during the first or second week, some of them not before the third week. Occasionally a faulty involution takes place, so that a second injection is required. The pustular and crustaceous syphilides behave more favourably, as they heal within a few days even if they extend over a large surface and though they have previously exhibited their malignant character by resisting mercurial therapy (see Plates II, III, IV and V).

Case 1.—Marie H., aged twenty-four. Treated at our division from January 3d to February 9, 1910, for a universal papular syphilide, by mercurial inunctions. At that time, the optic nerve on both sides was indistinct; venous hyperemia; optic neuritis (Dr. Fehr).

On April 13th, the patient was readmitted because of a dense papulo-crustaceous, rosette-shaped syphilide all over the body, varying in size from a dime to a nickel (see Plates XI and XII).

On April 19th, 0.3 gm. salvarsan. May 22d, the crusts were shedding. Healing took place in two to three weeks, leaving only slight pigmentations. May 19th, field of vision and background of eye, normal. Patient remained under observation until June 8th. Weight of body on April 23d, 110 pounds; May 1st, 115 pounds; May 15th, 119 pounds; May 20th, the same; May 25th, 122 pounds; June 4th, 125½ pounds

CASE 2.—Grete H., aged eighteen. In January 1909, primary affection of lip; mercurial inunctions for six weeks. On April 25, 1910, ulcerating, crustaceous papules on the back, nates and labia. Numerous spirochetes. On the head, ulcerations the size of a half dollar, extending to the galea. After the use of 112 gm. of unguentum cinereum (grey ointment), the ulcerations were only somewhat cleaner and somewhat reduced in size; the other efflorescences were also somewhat smaller, but not entirely healed. On May 26th, 0.45 gm. salvarsan; May 31st, efflorescences healed. Of the two ulcers on the head one had healed, the other being still superficial. June 7th, completely healed. Weight of body on May 29th, 117 pounds; June 7th, 119 pounds.

The micropapular and lichenoid exanthemata, which resist mercury stubbornly, also heal quite rapidly under this treatment:

CASE.—Ida H., aged twenty. Eight weeks ago, lesion on the labia and pudendum. At present a dense, universal, very tough micro-papular, lichenoid exanthem, which according to experience, usually resists treatment. General adenopathy; specific angina; plaques of the tongue; papules on the labia majora.

On April 19th, 0.3 gm. salvarsan. April 22d, distinct involution. May 26th, papules had healed; distinct recession of the exanthem; plaques also healed. The retrogression proceeded steadily, so that after three weeks a few small pigmented areas remained on and below the level of the skin.

The proper domain of the new remedy however, is to be found in the ulcerous, malignant forms of syphilis of the skin and mucous membranes. From the large number of my cases the following may serve as an illustration:

CASE 1.—H. E., aged twenty-five. Early in December 1909, chancre on the penis. In January 1910, a pustular eruption appeared. In Chemnitz, nine injections of salicylate of mercury were administered without much success. In the middle of May, treatment with packs and electric baths. Thereupon the condition became worse, marked by the development of extensive ulcerations. Iodoform ointment, sun-baths and homeopathic treatment, without the least benefit. Admitted to the Virchow Hospital on August 19, 1910. The skin of the entire body was covered with reddish-brown efflorescences, varying in size from that of a lentil to the palm of the hand; they consisted principally of large ulcerations surrounded by circularly concentric scales, shaped like oyster-shells. On the scalp there were deep ulcers extending to the galea and the left nostril was almost destroyed by a crust-covered ulcer. Practically no swelling of the glands. On the left side of the penis there was an oblong and somewhat oval-shaped chancre scar, about two to three c.m. in length. To begin with, all crusts were

removed by the application of macerating, keratolytic remedies and baths. On August 20, 1910, an injection of 0.5 gm. salvarsan was administered. Within three days, the effect became apparent; the ulcerations began to granulate from the margins towards the centre, and on September 1st all of the ulcerations were covered with new epidermis. The general condition of the patient has improved considerably; increase of the body weight from the date of the injection to September 22, 1910, has been fourteen pounds (see illustrations, pages 30 and 31).

CASE 2.—Minna L., aged twenty-three, was treated in our service with inunctions for primary and secondary lues, from February 17 to April 1, 1910. Towards the end of April an eruption reappeared on her body and on May 6th she was readmitted with deep, ulcerating, crust-covered efflorescences, the size of a dime and even larger, on her face and body. At the same time the mouth and throat exhibited deep, slimy ulcerations; the uvula was destroyed on both sides near the base, so that it hung from a mere thread of tissue and it was apparent that it would be a total loss within a few days. For days the patient was suffering such pain that she was unable to swallow and it was rather difficult for her to breathe. On May 10th, 0.4 gm. salvarsan was injected. Within two days the condition improved greatly; on May 18th, the throat had healed completely and the syphilide was covered by a scar. At present there are only small pigmented areas.

CASE 3.—Arthur P., aged twenty-three. Primary affection seven months ago; eruption four weeks later. From November 28, 1909, to the middle of March 1910, was treated with thirty-five injections of salicylate of mercury and calomel. For the past three months, pains in the joints of both knees. On May 5, 1910, the patient came to our division, very greatly debilitated. He had lost much flesh and resembled a skeleton; his skin had a deathlike pallor and his face resembled that of a corpse, with an expression of intense agony. All over his face and body he had crust-covered ulcerations, extending through the skin to the subcutaneous tissues, their size being that of a dime and larger; in addition to these there were numerous scars. A putrid stench issued from his nose, the septum of which was perforated, the left lower turbinate and the vomer being almost disintegrated. There were also extensive ulcerations in the nasopharynx and the left side of the uvula was practically destroyed. Because of the great pain he was unable to swallow and nutriment had to be administered by means of an esophageal tube. His pulse was very small and of poor tension rate, 120 and over. We were hesitant about administering an injection of salvarsan; when however, his condition continued to grow worse under iodipine injections and we expected him to die within a short time, we administered an injection of 0.4 gm. salvarsan, on May 21st. There was no rise of temperature and but moderate pain. Within two or three days his general condition had distinctly improved. On May 26th, healing was visible everywhere. On May 30th, the uvula had healed; the ulcers had improved considerably and some had completely

H. E. Before Treatment with Salvarsan (page 29).

H. E. After Treatment with Salvarsan (page 28)

H. E. Before Treatment with Salvarsan (page 29).

H. E. After Treatment with Salvarsan (page 28)

disappeared. The diseased nasal bone had been totally expelled and the fetor had disappeared. At the present writing, June 7th, the patient is much improved; he is commencing to swallow and is able to walk about. Weight of body, May 21st, 91⅓ pounds; May 28th, the same; June 5th, 93 pounds; June 20th, 108 pounds.

CASE 4.—H., aged thirty-five. Bank messenger (ophthalmologic service of Dr. Fehr). The condition of this man was very poor. Infected late in 1909. In January 1910, received twelve injections and KI. In March, very feeble, with commencing ulcerations in the throat. Vapour baths. Admitted on May 3d, with essential shrinkage of the conjunctiva. Numerous impetiginous syphilides on the scalp. Crust-covered ulcerous syphilides all over the face, trunk and extremities. The uvula is completely gone; the throat very much infiltrated and swollen, and the free parts present ulcerations covered with a slimy, false membrane. Albuminuria. On May 24th, 0.4 gm. salvarsan. Within six days everything clear, syphilides healing well; patient feeling well, beginning to swallow and able to be about. On June 13th, everything healed. Albumin disappeared. Weight of body on May 29th, 110 pounds; June 20th, 115.5 pounds.

Because of a swelling and tenderness on one of the tibiæ, both of these severe cases of malignant lues were reinjected with 0.5 gm. salvarsan, on July 26th. In both instances success was rapid. The first case was completely cured on October 25th, but the Wassermann reaction was still positive. The second has again developed a periosteal thickening on the lower end of the humerus.

It seems to be quite a constant rule that the paramount effect of the remedy is shown in periostitis and in cases of severe bone pains, which often drive patients to despair.

CASE.—A very sensitive patient, who had been suffering from periostitis of the ulna for five years, presented large swellings at the distal end of the bone; a radiograph (see page 33) showed the presence of severe periostitis and a deep ulcer of the bone; all methods of treatment had been employed without relief.

Although the intragluteal injection of salvarsan caused him much pain, he stated that the night after the injection was his first restful night in five years. Another patient, suffering from a nodular syphilide of the skin, which had resisted vigourous treatment with mercury and arsacetin, declared that for a year and a half he had had such severe pains in the tibiæ every night that he had injured his teeth as a result of biting them. He had previously suffered from very severe and painful inflammatory joint rheumatism, but the pain experienced at that time did not compare with these nocturnal bone pains. During the second night after the injection, he was entirely without pain! A third patient of herculean build, had been infected with syphilis and malaria while in the tropics eight years ago; he had undergone continuous antisyphilitic treatment with mercury and iodine,

Radiograph in a case of severe periostitis with deep ulcer of the ulna (page 32).

and once also with atoxyl, but he was still suffering from swellings of the cranial bones, which gave him such severe pain that he injected 3 gm. (!) of morphine daily. During the very night after the injection his pain completely left him, so that on the second day he went without permission to the Hoppegarten race-track and decreased his daily dose of morphine voluntarily. A gumma, the size of a small apple and situated typically at the sternoclavicular joint, was entirely absorbed within two days.

This sudden disappearance of pain at a certain hour, can only be explained by a destruction of the spirochetes, inasmuch as the conspicuous symptom of pain in the bones during the night can hardly be assumed to be anything else than a biologic manifestation of these parasites.

Visceral Lues.—The following case of visceral lues observed through an extended period, is highly interesting:

Frederick K., aged thirty, was treated from March 2d to April 10th, for a papulo-ulcerous syphilide, which had already been treated with mercury, iodide of potassium and arsenic, at the out-patient clinic of Professor Buschke. Subsequently he was treated homeopathically and from March 11 to April 30, 1910, he returned to the clinic of Professor Buschke, with an ulcer the size of a half-dollar on his back, similar ulcerations behind his ears and upon his head, a swelling of the tibia and a tumour the size of a hen's egg in the left testicle. The patient's condition was badly run down and his temperature was 102° F. He improved under a course of inunctions. On April 12th, his lower jaw commenced to tremble and he was unable to talk. He had suffered from similar attacks during the previous year. On April 30th, the patient was discharged, much better. Eight days later the ulcerations broke out again and his physician (Dr. Adler) sent him to the hospital because mercury did not agree with him, and levico,[1] which had been prescribed for him, produced but little effect. Aside from the symptoms mentioned, he suffered from headache and his skull was very sensitive to pressure. On May 21st, 0.405 gm. salvarsan was given. The temperature rose to 102.5° F.; May 28th, the ulcers had completely healed. June 5th, the testicle was of normal size and consistency. Dizziness had completely disappeared, also sensitiveness of the skull to pressure. Weight of body May 16th, 143 pounds; June 3d, 145 pounds.

The patient's condition continued to improve; and although a physician had pronounced him permanently unfitted for work, in September he was vigourous and able to work, having gained twenty-five pounds in

[1] A mineral water. [Ed.]

weight. As there was still a + Wassermann reaction, a second injection was given.

In two cases of epilepsy following lues the attacks ceased, but the patients were not under observation a sufficient length of time. One case of recent peripheral facial paralysis in the secondary stage was cured in a few days; one case of trochlear paralysis and one of abducens paralysis (a recurrence after an injection of salvarsan) quickly improved.

I have seen early icterus and late specific icterus disappear after a few days.

Syphilitic growths of the larynx, resulting in asthma and stridulus of such a severe degree that the patient had been sent to Privy Councillor Hartmann's service for tracheotomy, rapidly disappeared, leaving only a few large infiltrated masses which were treated by the application of a second injection four weeks later. Edema of the larynx which we feared at first, did not occur. Two cases of cerebral lues, with development of a tumour, tolerated the injection very well, although the symptoms were very grave; also in two cases of recent luetic apoplexy and in another case several weeks old there were no evil effects, marked improvement accompanying these cases.

The following report of the case of a patient, notes being carefully taken after continued ocular inspection by Fehr, shows how rapidly and efficiently the remedy acts upon syphilitic processes in the brain:

E. H., thirty-five years old, bookkeeper, infected in 1899, treated with mercury injections for almost half a year. In 1904, he had right diplopia, as well as abducens paralysis, declared to be of severe grade by a high authority. This was treated with prisms of 6, 8, and 10 bases, and cured. In April 1907, the abducens paralysis reappeared and improved after the same treatment. Quoting the patient: "In the spring of 1908, I observed that the visual power of my right eye was decreasing, while my left eye remained excellent. Privy Councillor S. stated that the pupil had lost its reflex. Treatment with iothion and sajodine had a detrimental effect upon me. My right eye did not improve. To the contrary, newspaper print appeared very small when I closed my left eye and it was blurred besides. Being discouraged, I wanted to continue working as long as I could and then commit suicide, if I should lose the sight of my left eye, the condition of which also deteriorated as a result of the continued strain upon it.

"I continued at my occupation and although my work is very tiresome for my eyes, I have been working with my left eye exclusively during the last year and a half.

"On June 21st, it was found (by Dr. Fehr) that loss of pupil reflex with

accommodation reaction, had taken place, with slight abducens weakness in both eyes, more so in the right than in the left; otherwise motility good.

"On July 5, 1910, 0.55 salvarsan was injected.

"July 8th, slight pupil reaction and penetration of light.

"July 10th, I could not notice any improvement in regard to the eye. The astonishing change took place during the night, between July 10th and July 11th. On July 11th, I was able to see newspaper print and the skyline of houses tolerably clearly.

"July 11th, distinct pupil reaction to light.

"July 15th, pupil reaction very inactive, but *clearly present* (*without light!*); fundus normal.

"To-day I can see very well with my left eye, the sight of the right eye being tolerably good for objects at a distance. I can easily read newspaper print and written script, although it somewhat strains the eye and the outlines of the letters still have a slight shadow. But I still notice a daily improvement, as the injection was applied on July 5th and to-day is only July 17th."

Of course success depends upon whether or not syphilitic infiltrate is present alone, or whether degenerative processes have already occurred. More extensive observations have been made in this connection, particularly by Alt, F. Lesser, Treupel, Gennerich and others, to be described hereafter.

The Eye.—The examinations of the eye were made by Drs. Fehr and Seeligsohn, the latter reporting as follows:

Of the two hundred and fifty cases investigated ophthalmologically by Dr. Seeligsohn previous to injection, there were:

I. Twelve cases of primary syphilis.
II. One hundred and twenty-four cases of secondary syphilis.
III. Seventy-seven cases of tertiary syphilis.
IV. Thirty-four cases of metasyphilitic affections.
V. Three cases of infantile hereditary syphilis.

I. In all the primary cases, the pupils reacted promptly; but neither in Groups I nor II could a roseola of the iris (Krückmann) be observed. Aside from anomalies of refraction and old corneal opacities, the results found with the ophthalmoscope were normal; likewise tests for vision.

II. In one hundred and eight of the one hundred and twenty-four cases of secondary syphilis no specific changes had taken place; however, we observed the following:

In six cases, inequality of pupil with retarded pupil reaction, mostly from four or six months to one year after the infection.

In one case, inequality of pupil and monocular rigidity to light.
In two cases, double rigidity to light, but the reaction to accommodation was normal.
In one case, vascular changes in the retina after a two years' illness.
In one case, recent peripheral syphilitic chorioiditis.
In one case, recent central syphilitic chorioiditis.
In one case, recent papular iridocyclitis.
In two cases, vigourous central myopic chorioiditis.

III. In fifty-eight of the seventy-seven tertiary cases, the eye did not show any specific changes; however, we observed:

In fifteen cases, disturbed pupil reaction, such as inequality, absence of reflex or considerable diminution of reaction to light, some of them showing presence of accommodation; two of these cases had been complicated for several years with incomplete ophthalmoplegia, and in one of the cases the other eye also showed total ophthalmoplegia.
In one case each, changes in the vessels of the retina, peripheral chorioiditis and the remains of an iritis.
In one case, complete optic atrophy in one eye and progressive optic atrophy in the other.

IV. Among the thirty-four metasyphilitic patients there were:
Thirty with tabes dorsalis.
Four with incipient paralysis in the period of remission.

Most of the thirty cases of tabes exhibited the typical symptoms of the disease more or less; in only four cases—and two of these were in the first stage—the pupil reaction was present in the remaining cases, the light reflex had either entirely disappeared or it was considerably diminished; in eleven cases accommodation had also disappeared and in nineteen cases there was an inequality of the pupils.

Apart from the refractive anomalies, vision was normal in all of the cases. Paralysis of the ocular muscle was observed three times. In one case there was complete atrophy and in a second case incipient atrophy of the optic nerve; while in a third case, one eye had complete, the other progressive atrophy of the optic nerve.

In one of the four cases of paralysis the affection being very recent, the eyes were found to be normal; in the second case, the pupil reaction was greatly diminished; in the third case, there was beginning inequality

of the pupils; and in the fourth case, there was incipient atrophy of the optic nerve (case of E. H.).

V. Of the three cases of hereditary syphilis, in all of which parenchymatous keratitis was present, the ophthalmologic examination could not be made in one of the cases; the cases of the other two, i.e., M. L. and A. G., will be reported in detail later on.

In seven cases, the patients had been previously treated with atoxyl, arsacetin and other arsenic preparations. In not a single instance did any ocular changes take place after the injection.

In none of the cases in which examinations as to the pupil reaction were repeatedly made after the injection were changes recorded; rigid pupils remained rigid, and paralysis of the ophthalmic muscles which had lasted for several years, remained unchanged.

But Fehr and Seeligsohn observed a very favourable effect in cases of episcleritis and iritis. The following case of papular iritis deserves to be mentioned:

Elise H., aged thirty-one, saleslady, married five years without issue, experienced pain in her throat towards the end of February 1910. On March 3d, Dr. Nast found: Ulcer on the right tonsil, indolent swelling of the submaxillary glands (primary affection). As the Wassermann reaction was positive, a course of inunctions was administered. On April 19th, in spite of 125 gm. of grey ointment, new ulcers developed near the uvula and pain in swallowing. With iodide of potassium, gradual improvement of throat trouble. No roseola. On June 23d, the patient complained to Dr. Seeligsohn of pain and disturbed vision in the right eye. *Status præsens:* Strong pericorneal injection, cornea dull, pupil contracted, iris vascularized, a grey mass in the pupillar region; iridocyclitis. Received at the private clinic. Therapy: Atropine five times daily; grey ointment, 3.0 gm. On June 28th, cornea a little clearer, pupil but little larger, the grey mass of exudate in the pupillar region increased in size; prompt refraction and projection of light. July 3d, gradual absorption of the exudate, the latter decreasing in size from the margin inwards; grey ointment, 4.0 gm. July 7th, exudate mostly absorbed, still a grey spot laterally; medial circular turbidity, pupil somewhat larger. In the upper corner of the chamber, a small reddish tumour. Thus far, 42. gm. grey ointment. Iodide of potassium, 15.0: 200.0, one tablespoonful three times daily, per anum. July 10th, pericorneal injection more marked; iris is still vascularized, exudate much smaller. The tumour projects to the middle of the iris. No red reflex, prompt refraction and projection of light. July 14th, pericorneal injection much stronger, cornea looks angry, numerous spots arranged triangularly on Descemet's membrane; pupil of medium width, iris more markedly vascularized, still numerous synechiæ. The tumour has con-

tinued to grow and projects to the edge of the pupil, with an oval convex rim. The exudate upon the anterior capsule of the lens is just visible, but to-day there is also a small exudate on the floor of the anterior chamber. Thus far, 60 gm. grey ointment and two injections of salicylate of mercury. On July 15th, injection of salvarsan. July 16th and 17th, the small exudates on the floor of the anterior chamber absorbed; otherwise condition unchanged. July 18th, the size of the tumour is somewhat diminished. July 20th, the efflorescence on Descemet's membrane also appears in the upper part; vascularization of the iris decreased. The tumour still visible. Patient counts fingers at twenty inches. July 27th, injection a little less, exudate on the anterior capsule has disappeared entirely; fingers at thirteen to sixteen feet. August 4th, injection still less, efflorescences on Descemet's membrane much diminished; iris not vascularized, markings distinct; numerous synechiæ of the pupil, the latter of medium width. Papillæ indistinctly visible, turbidity of the vitreous body. Vision 1/6. Vapour treatment. August 12th, efflorescences very fine, turbidity of the vitreous body, papillæ visible, but not clearly. Vision, 6/36+ Sph. 3.0=6/12. August 13th, discharged, improved. September 19th, still some fine efflorescences on Descemet's membrane and anterior capsule of the lens, pupil of medium width, flakes on the vitreous body, margins of papillæ faded. September 24th, with correcting glasses, vision = 6/10. November 2d, still fine efflorescences on Descemet's membrane, vitreous body clearer, margins of papillæ slightly faded. Vision = 6/10.

Consequently we have here a patient suffering from extragenital syphilis who developed a severe iridocyclitis, in spite of vigourous inunction treatment. A new mercurial treatment and iodide of potassium failed to prevent the growth of a large papule from the ciliary portion of the iris and a marked exaggeration of the ocular affection. On the other hand, the tumour began to decrease two to three days after the injection of salvarsan and it disappeared entirely four days later; the iridocyclitis gradually disappeared, so that the patient could be discharged on August 13th, with a vision of 1/2. Therefore the injection proved to be an excellent remedy in this case, where mercury and iodide of potassium had failed.

Fehr and Seeligsohn observed considerable improvement in the turbidity of the vitreous body and consequently improved vision in several cases of syphilitic chorioiditis. The chorioidal foci were absorbed one after the other.

Seeligsohn's records in two cases of syphilitic parenchymatous keratitis read as follows:

Case 1.—Marianne L., aged five, daughter of a police official. Father treated for syphilis with mercury several times; mother always healthy. The

child had been healthy up to this time; never had any eruption. For fourteen days, both eyes had been inflamed; the glands of the throat were slightly enlarged, indolent, moderately hard. On July 12, 1910, decided photophobia of both eyes developed; pericorneal injection, entire cornea dull; pupils contracted, background not visible. Diagnosis: Hereditary syphilitic parenchymatous keratitis. Treatment: Atropine, three times daily. On July 14th, injection of salvarsan. July 18th, pupils of moderate width, prompt refraction and projection of light. July 21st, marginal portions of cornea a little clearer. July 25th, the cornea is a little clearer at the right margin also. August 1st, right marginal parts are no longer as saturated as they had been; on the left side, the corneal periphery is entirely free, the centre less turbid. The child recognized large objects at one yard. On August 8th: Right eye, the central opacity is no longer diffused, but single, thick spots are visible; left eye, beginning vascularization from the lateral margin. The patient sees large objects at thirteen feet. August 15th, on both sides the marginal parts are perfectly clear, the central turbidity being much finer on the left and a little thicker on the right side. August 25th: Left eye, the middle portion of the cornea is entirely clear, except for flake-shaped areas of haziness, remaining only in the centre and in the lateral part. Finger visible with both eyes at sixteen feet. September 16th, photophobia disappeared, eyes no longer inflamed. Right eye, several large and small turbid spots in the centre and the periphery; left eye, a central turbidity. On both sides, papillæ quite red, margins free; vision 6/8 (?); October 5th, right, 6/8 (?) left, 6/6 (?). Periphery of chorioid and retina free.

Case 2.—A. G., aged ten, daughter of a merchant. Father died of heart disease. Mother infected about seventeen years ago, treated with several injections of mercury; had had three still-born, macerated children, previous to the birth of the present patient, and subsequently another child, healthy to date. Six years ago the mother suffered from a gumma of the clavicle, which responded fully to inunctions and iodide of potassium. At present, the Wassermann reaction is strongly positive. The patient herself is declared to have been healthy up to present time. Six weeks ago, whooping cough was followed by inflammation of the left eye, which was treated with atropine and iodide of iron; Wassermann reaction strongly positive. *Status præsens:* On July 10th, decided photophobia and lachrymation on both sides. Left eye: Pericorneal injection, entire cornea of a porcelainlike opacity; in the centre, a still more marked greyish-yellow infiltration, ½ inch long and ¼ inch wide; pupil contracted; iris but faintly visible, prompt response to light. Right eye: Lateral part of cornea hazy. Treatment: Atropine three times daily, on both sides. On July 11th, injection of salvarsan. July 14th: Left eye, marginal portions of cornea a little clearer; the central infiltration has more of a greyish colour to-day, vascularization taking place from the margin. Right eye: Cornea completely hazy, as though it were breathed upon. Right eye, motion of hand visible at one yard; left eye, only responds to

light. July 21st: Right eye, medial portion of cornea more hazy and spotted, but more uniformly in the lateral portions. Hot-air douches. July 29th, grey ointment 2.0 gm. daily, as the condition of the eyes is changing but little. August 4th: Left eye, the corneal injection is somewhat lessened, the cornea being somewhat clearer in the medial portions, but still very hazy laterally and in the centre. Right eye, *status idem*. August 12th, the cornea is vascularizing from the medial margin. Left eye, the cornea somewhat clearer also in its lateral part, fingers visible at half a yard. During the next three weeks the situation changed but very little, in spite of continued inunctions (thus far 60 gm.). Photophobia and pericorneal injection gradually decreasing, the opacities of the cornea are almost unchanged. September 2d, a second injection of salvarsan. September 9th, photophobia disappeared entirely; very little pericorneal injection. Right eye: The cornea is well vascularized and is beginning to clear up from the margin. Pupil wide, fingers visible at five feet. Left eye: The medial part of the cornea is perfectly clear, the lateral part still slightly hazy and the thick infiltration in the centre is a little thinner. Fingers visible at thirteen feet. September 17th the treatment was stopped, the patient departing for her home. October 25th, letter received, stating that vision had improved considerably.

While improvement was rapid in one of the cases, in the other which was a very grave one, the first injection could not prevent the second eye from becoming affected. This is a common experience with the mercury treatment. Nor did the second injection result in any considerable degree of success. The conditions of vascularization probably play an important part in this connection, inasmuch as the remedy's successful attack depends upon them. These observations also correspond to those made by von Uhthoff and v. Grosz.

Fehr also observed a surprising improvement in one of two cases of congenital syphilitic parenchymatous keratitis. Three days after the injection, photophobia and irritation disappeared; and the eyes which had been kept closed spasmodically for weeks, opened spontaneously. From this moment too, the clearing up of the cornea commenced. But in the second case on the other hand, a favourable effect was not apparent for some time after the injection although there was a gradual improvement in this case too. Whether however, this improvement is to be attributed to the salvarsan or to the subsequently administered inunctions, it is hard to say.

Fehr reports an exceptional case of shrinking of the conjunctiva in which the process of shrinking ultimately progressed to almost complete ankyloblepharon; other conditions were quite satisfactory (compare above, page 32; case of H., bank messenger, aged thirty-five).

Effects Upon the Healthy and Unhealthy Optic Nerve.—The effect upon the optic nerves is of the utmost importance. Following the administration of atoxyl (also arsacetin), according to the compilation by Igersheimer, thirty-seven cases of amaurosis are recorded (*Archiv f. Ophthalmologie*, Bd. LXXI, 2 Heft). As a result of his investigations he states:

Atoxylamblyopia, when appearing in man in an overwhelming majority of cases, is simple, progressive atrophy of the optic nerve, the papilla either fading very soon or very late. It is only in exceptional cases (two treated by Fehr) that the amblyopia is stationary and presents the aspect of retrobulbar neuritis. Only one dissection upon a human body has so far been reported (Nonne), and in this case the most pronounced changes of the optic fibres in the vicinity of the chiasma were observed; these changes are purely parenchymatous. Experiments with local applications of atoxyl upon the eye of the rabbit have shown that the injection of small and medium amounts of the poison into the vitreous humor and under the conjunctiva causes a degeneration of the nerve-tissue only. When atoxyl was injected subcutaneously into dogs and cats, processes of degeneration appeared in the inner layers of the retina and in the optic nerve. In cases of chronic poisoning, the change in the condition of the medullary sheath of the optic nerve, known as the "Marchi reaction" (Schreiber), is clearly apparent. When atoxyl injections were made in experimenting with cats, marked nervous phenomena were observed and the anatomic investigation revealed very grave changes in the cells of the brain and spinal marrow, with maximum localization in the optic thalamus. An isolated degeneration of the retinal ganglion was observed in a rat, poisoned subcutaneously; also a moderate diffused Marchi decay of the optic nerve, particularly near the chiasma. Amblyopia caused by atoxyl, takes a totally different and characteristic clinical course in man than amblyopia caused by arsenic and the anilines. It has been shown by chemical research that most of the atoxyl introduced into the body circulates in the blood without being decomposed, then to be eliminated; also that small quantities of inorganic arsenic are separated from the atoxyl molecule. The atoxyl which has not been broken up, either remains as such or is eventually transformed by the cells, to which it is anchored into its far more poisonous reduction products. In cases of pronounced chronic atoxyl poisoning, the amount of inorganic arsenic which has been set free, may also produce a toxic effect. Chemical investigations have shown that in the bulb very strong affinities exist towards the atoxyl molecule, but not towards inorganic arsenic.

From the experiments made in animals by Ehrlich, it would appear

that this danger might not follow the use of salvarsan, as its affinity for the nerve-tissue of the centre of vision seems to be of a different character. A series of aromatic derivatives of arsenic produces peculiar disturbances of coordination in mice, causing dancing motions; the latter are attributed to disturbances in the vestibular nerve, according to investigations made by Roethig ("Untersuchungen am Zentralnervensystem von mit Arsacetin behandelten Maüsen," *Frankfürter Zeitschrift für Pathologie*, Band III, Heft 2). In some of these animals Roethig also observed a decided degeneration of the optic tract, and thus all similar preparations must necessarily arouse the suspicion that they will produce disturbances in the optic nerve of man also. As this is not the case with salvarsan, it was hoped that it would not injure the normal retina. The fear was so great in this regard that there was considerable hesitancy about taking up the new remedy in most of the clinics. This fear was still further increased by unfounded rumours about an amaurosis produced by salvarsan. In more than twelve hundred cases we observed no such condition, nor any other injury to the eye, except in two instances where the patients saw flashes of light and darkness before their eyes for a short time; and not even in the large number of cases estimated at twenty thousand, in which salvarsan has been injected, has any similar instance been reported. It is hardly probable that amaurosis could be concealed. Fehr who has investigated a large number of my own cases, has never observed that the sight of any patient was injured by the injection. However before making an injection, the condition of the background of the eye should be carefully investigated, so as to avoid the oversight of any existing neuritides, which might cause blindness later on, thus relieving the remedy of any responsibility for subsequent complications. During the course of these regular investigations of my records and cases, Fehr has found only two per cent. of abnormal optic nerves; he has also found neuritides, choked disc and retrobulbar neuritis in cases of eruptive and fresh secondary syphilis, without subjective optic disturbances. It is not improbable that the incomplete healing of such syphilitic neuritides may lead to subsequent processes of degeneration in the optic nerve.

Nevertheless hypersensitiveness might be present in rare and exceptional cases. It might happen particularly that cases previously treated with atoxyl might suffer from a latent injury to the optic nerve or the retina, which might become progressive through the administration of salvarsan. However, I have injected twelve cases which had been previously treated with atoxyl or arsacetin, without any injury. While at first

we excluded from treatment all affections of the optic nerve, some doubtful cases were treated later on without injury. In the very first of my communications I was able to report the following case:

Marie H., aged twenty-four years. From January 3d to February 9, 1910, was treated with inunctions in our service, for universal papular syphilides. At that time both optic nerves had indistinct margins, venous hyperemia; optic neuritis (Dr. Fehr).

On April 13th, the patient was readmitted for treatment with dense, papular, crusty, rosette-shaped syphilides, the size ranging from that of a dime to a quarter, which were distributed all over her body.

On April 19th, 0.3 gm. salvarsan. May 22d, the crusts had disappeared; healing in two to three weeks, leaving only pigmentation. May 19th, field of vision and background of eye normal. Remained under observation till June 8th. Weight, April 23d, 110 pounds; May 1st, 115 pounds, May 15th, 119 pounds; May 20th, 119.3 pounds; June 4th, 125 pounds. Patient discharged with full power of vision.

Since then I have treated two similar cases with the same success. Later on, however, cases of incipient optic neuritis were also treated with salvarsan.

Case 1.—Karl K., travelling salesman, aged thirty-nine (referred by Dr. H. Feilchenfeld). In December 1909, primary chancre and inguinal adenitis. In January 1910, roseola appeared. In March, affection of the eyes, in spite of the administration of thirty-eight injections of bichloride; from April until June, about sixty inunctions and iodide of potassium. On August 12th, Professor Oppenheim pronounced the case cerebral syphilis, while Dr. H. Feilchenfeld's diagnosis was "diffuse opacities of the vitreous body and neurochorioretinitis." August 13th, skin, mucous membranes and glands, negative; Wassermann reaction strongly positive. Salvarsan injection. August 20th, examination by Dr. H. Feilchenfeld. Objectively: same as above, although the patient says vision is improved in the right eye, worse in the left. September 29th, vitreous body considerably clearer, border of papillæ more sharply defined, visual power almost normal. October 6th, the Wassermann reaction still being strongly positive, a second injection of salvarsan was administered. October 11th, opacities still present on the vitreous but less numerous and much finer.

Case 2.—Bernhard I., clerk, aged twenty-five. In August 1909, primary chancre followed by roseola; energetic courses of mercurial treatment administered several times. Because of disturbed vision, was given vapour treatment and iodide of potassium at the Charité for three months, and was then treated with inunctions at a private clinic. In the spring of 1910, the patient moved to Mülheim-on-the-Ruhr, where he was treated by Dr. Stuelp, whose examination

made on February 7, 1910 showed the following: Specific optic neuritis, with incipient atrophy, temporal fading, particularly on left side; central colour scotomata. Vision: Right, 5/60. Sph.—2. D ⊂ Cyl-1. D = 5/12. Left, 5/60. Sph.—2. D = 5/15. Wassermann reaction positive. March 31st received at the clinic. Six courses, 4 gm. mercury daily. Gradual improvement of vision which then became normal; neuritis improving also, small colour scotomata remaining. On April 19th, the patient was discharged in an improved condition. Readmitted on May 7th, as new mucous patches appeared in the throat; mercury, Zittmann, etc. In spite of this treatment, vision became worse on June 15th. With the aid of correcting glasses, vision was only 5/10 on both sides. Central colour scotomata. Ophthalmoscopic examination same as before. August 30th vision only 3/10. A black spot in the macula. Patient was transferred to me by Dr. Stuelp. August 31st, skin intact, patches on the tip of the tongue and the upper gums; isolated papules on the shaft of the penis. Low-grade general multiple adenitis; Wassermann reaction positive. On September 1st injection of salvarsan. After a few days patient returned to Mülheim. September 8th, Dr. Stuelp reported: Right, 5/50; left, 5/25. Colour scotomata improved. September 25th, right, 5/6; left, 5/10. Central colour scotomata absent; optic nerve of decidedly better colour, macular spot being absorbed. October 17th, right, 6/5; left, 5/5 (?). Colour scotomata absent.

In this case the disease at first improved considerably under mercury, and subsequently mercury no longer had any effect, the conditions having become steadily worse. Salvarsan, on the other hand, after a temporary set-back brought about a considerable improvement.

This case also illustrates the observation that salvarsan is particularly effective in those cases in which mercury is of no avail.

In a very severe case of degenerative choked disc Fehr also observed considerable improvement after the injection.

I have also assumed the risk of administering the injection in eight cases of advanced atrophy of the optic nerve, the patients being almost blind. The patients having been informed by their eye specialist and myself of the possible dangers of such an injection, I undertook this treatment at their earnest solicitation, hoping to stop the further advance of the process in some of the cases. Not one of these cases became worse.

As a result, I was encouraged to administer the injection in more recent cases, in which according to the specialists' opinion, a favourable prognosis was to be anticipated and whenever the patients agreed to the procedure, after having been fully informed of the dangers that might accrue.

CASE 1.—Heinrich W., aged thirty-three. Infected in 1901; treated with injections and pills of mercury and iodide of potassium. Since 1902, lancinating pains in the legs, difficult urination, diminution in the power of vision. For the past two weeks, blind on the left side and vision considerably impaired on the right side. September 26th, skin, mucous membranes, glands and genitals negative. Patellar reflexes present; Romberg indicated.

Ocular conditions (Dr. Seeligsohn): Loss of pupil reflex to light, accommodation unaffected. Optic nerve atrophy: Left side, complete; right side, progressive. Vision: Right = 1/2, left = 0. Field of vision for white normal, considerably restricted for colour. Injection of salvarsan. October 10th, report of Dr. Poduschka, eye specialist at Gablonz: Vision, 5/10 to 6/10. General condition good.

CASE 2.—Ferdinand H., aged forty-nine, merchant. Patient denies syphilis. Married 1894; one still-born, macerated child; one miscarriage. After repeated courses of inunctions having been administered to husband and wife, two healthy children were born. In August 1909, incipient paralysis (illusions of grandeur). After having been treated at an institution for several months complete remission took place, which has remained permanent thus far. Wassermann reaction negative. September 7th, condition of eyes (Dr. Seeligsohn): Loss of pupil reflex to light and accommodation. Left coloboma, inward and downward (old lesion). Both pupils pale, vessels rather narrow, myopia of 4 to 5 D. Field of vision somewhat restricted for white, very considerably for colours. Power of vision with correcting glasses, right, 3/4; left, 2/3 (?). Salvarsan administered on September 13th. October 15th, pupil reaction unchanged; power of vision, right, 3/4; left, almost normal. Field of vision for colour considerably widened.

CASE 3.—Jacob R., aged forty-nine, compositor. About fifteen years ago had chancre and exanthem; treated with inunctions and injections. For the past two years, the patient felt unsteady on his feet; he complained of pain in the finger-joints and in the back, numbness in his arms, girdle sensation, loss of weight, urinary incontinence. He was a man of moderate strength; skin and mucous membranes negative; no adenopathy. His walk was somewhat ataxic, patellar reflexes extinguished; Romberg indicated. Diagnosis: Tabes dorsalis. Wassermann reaction positive. July 30th, condition of eyes (Dr. Seeligsohn): Right pupil wider than the left. Loss of reflex and light, but not to accommodation; atrophy of optic nerve, particularly on the right side (lateral parts of papilla pale). Vision, with correcting glasses, both sides, 6/5. Field of vision free for white, very limited for colour. Right, green above and below to 8°; left, above and below, 10°; lateral, 15°; medial, 12°. August 9th, injection of salvarsan. August 14th condition unchanged. September 17th visual tests: Pupil reaction and ophthalmoscopic findings unchanged; field of vision for colour considerably wider. Right, green above; lateral and medial to 20°; below, 10°; left, medial and below, 20°; above, 15°; lateral, 25°.

V. Grosz (*Deutsche medizinische Wochenschrift*, 1910, No. 37) has pointed out that mercury acts unfavourably in atrophy of the optic nerve and he therefore also advised against the use of salvarsan. According to our experience, however limited it may be at present, this position does not appear to be justified. For though it does not follow from the subjective improvement of the patients that salvarsan may be considered a remedy for optic nerve atrophy, at least it seems to be demonstrated that in cases where an injection is desirable, it may be administered without fearing that the diseased optic nerve will be detrimentally affected.

Tabes and Paralysis.—As regards the parasyphilitic diseases, it is self-evident that degenerated portions of the central nervous system cannot be replaced. However according to Erb, other syphilitic lesions are found in tabes besides the sclerotic processes, especially in the blood-vessels, gummata and meningitic proliferation, this being also the case in progressive paralysis; for in many cases of tabes, as Adrian has shown, we also find manifest symptoms of syphilis upon the skin or in the internal organs. Of late however, many authors relying on the constancy of the Wassermann reaction, have been led to pronounce both of these diseases real syphilis. In addition, cases of pseudotabes and pseudoparalysis (Fournier) in which a correct diagnosis is often very difficult, are perhaps of more frequent occurrence than has been heretofore supposed. These cases give a better prognosis even with mercurial treatment. In view of the fact that salvarsan brings about a speedy cure of foci in skin affections which failed to respond after years of treatment with mercury, the use of the new remedy in tabes and paralysis appears to be perfectly justifiable. If for example in tabes, even very small foci can be made to recede, the advantage to the patient must be very great, as the most important nerve-tracts lie in close proximity in a very limited space. In fact we are of the opinion that generally speaking the new treatment is able to exert a favourable influence in many directions. The majority of patients declare that they have materially improved. Thus I have observed the rapid disappearance of serious intercostal neuralgia in two cases that required the constant employment of narcotics; the lancinating pains almost without exception disappear, or there is at least an improvement; gastric crises cease altogether or they become less frequent and less severe. In one case it was reported that weakness of the muscles of deglutition, existing for years and making it difficult for the patient to take solid nourishment was cured. Lost sexual power has been restored. In one case it was so greatly benefited that daily intercourse was imprudently indulged in; but even now

after three months under judicious control, the improvement is still present. Almost without any exception, ataxia is also modified materially. I have frequently observed all of these successful results continue for months although the lancinating pains would sometimes return. Nevertheless I have not been able to determine whether or not these are actually curative processes, but I certainly do not believe that the results are due simply to suggestion. This fact I consider to be demonstrated by the patients themselves. It is not until a number of days have elapsed that they report that the pains have disappeared, whereas they still complain of the pains for some time after the injection. In view of extensive subjective improvements, I no longer hesitate to administer injections, even in cases where the Wassermann reaction is negative. Undoubtedly an important part in this happy result should be attributed to the stimulating and tonic effect of the remedy. But we shall have to wait until it has been demonstrated that the success is a permanent one before it may be safely concluded that the remedy stops the progress of the disease. Objectively I have seen trophic ulcers on the sole of the foot disappear in two cases, one being of a rather mild type while the other was deep-seated and obstinate. Once it seemed that I noticed a return of the patellar reflexes, but I was mistaken. This error shows that great caution must be exercised in this respect.

CASE.—J. R., aged forty-nine, compositor (see page 40). For two years he has been unsteady on his legs, particularly in the dark; numbness in the extremities, pains in the fingers and the back; girdle sensation and from time to time, involuntary micturition. Objective symptoms: Slight ataxia, Romberg barely indicated, patellar reflexes absent. Right pupil larger than the left. Loss of pupil reflex to light, but not to accommodation. On August 8th, 0.5 gm. salvarsan. September 17th, pains and numbness disappeared. Unsteadiness in the dark considerably decreased; no more involuntary urination; slight ataxia and Romberg present. The patellar reflexes are distinctly present.

When it occurred to me that I might have been mistaken on my first examination in regard to the absence of the patellar reflexes, the patient who was greatly elated, informed me that Professor Oppenheim had also made the same observation several times previously; and when I made further inquiries the patient's statement was confirmed. But a subsequent examination made by Professor Oppenheim, revealed the fact that the patient simulated the patellar reflexes by auto-suggestion; that is to say believing them to be present he actually produced them! In cases of

advanced paralysis, I have not seen any absolutely positive improvement; in earlier stages a favourable remission seemed to take place in isolated cases. However, a positive opinion cannot yet be given. But on the other hand, in the case of syphilitics whose physical energies were depreciating, who were depressed and so forth, I observed distinct improvement on various occasions although I would not designate these cases as permanently cured.

Effect on the Wassermann Reaction.—Concerning the influence of salvarsan on the Wassermann reaction, Alt was the first to show that it is a very distinct and a vigourous one. The references in the literature in respect of the frequency of the change from positive to negative do not agree; in a great many cases however, the moment of the examinations has not been exactly timed. That it is of great importance to know this as well as the strength of the reaction the moment it begins, has been amply demonstrated by my assistant Dr. Lange (*Dermatologische Zeitschrift*, XVII, 7, 480 ff.). Lange examined fifty-one cases once or twice every week, observing them for a sufficient length of time and found that the reaction became negative in the majority of these cases.

A period of four to five weeks after an injection of salvarsan was considered sufficient for observation, as most of the cases had been rendered negative by that time. Furthermore the interesting fact was revealed that the period of time in which the reaction became negative generally depended less upon the clinical severity of the case than upon the incipient strength of the reaction before the injection was administered. The cases with complete inhibition (+ + + +) required an average of four to five weeks, while cases with a faintly positive reaction (+) took about eight days. In cases with an intermediate strength of reaction the time required would vary between these extremes.

Cases (Reaction) Rendered Negative

The occurrence of the negative reaction varies between one and seven weeks, apparently with very great differences (see table, page 50). When however, the cases are arranged not according to the severity of the clinical picture, but according to the incipient strength of the reaction preceding the treatment, even the limited clinical material at our command presents a surprising relationship between the period leading up to the appearance of the negative reaction and the strength of the reaction before the injection.

Cases Rendered Negative

No. of Case[1]	Incipient Strength of the Reaction	Course of the Reaction	No. of Weeks Required to Make W. R. —
		18/IV. 22/IV. 25/IV. 30/IV. 6/V. 12/V. 18/V. 22/V. 23/V.	
9	++++	++++ ++++ +++ +++ ++ ++ − − −	5
		3/V. 12/V. 22/V. 31/V. 7/VI. 12/VI.	
14		++++ ++++ ± − − −	4
		17/V. 25/V. 31/V. 2/VI.	
15		++++ − − −	1
		30/IV. 7/V. 12/V. 23/V. 2/VI. 7/VI.	
32		++++ ++++ ++ + ± −	5
		19/IV. 30/IV. 7/V. 15/V. 20/V. 23/V.	
33		++++ +++ + − − −	4
		28/IV. 30/IV. 7/V. 12/V. 15/V. 20/V. 23/V. 2/VI.	
34		++++ ++++ +++ ++++ ++ ++ − −	4
		7/V. 12/V. 15/V. 20/V. 23/V. 2/VI. 18/VI.	
36		++++ +++ ++ ± − − −	2
		2/IV. 7/V. 15/V. 23/V. 18/VI.	
51		+++ ++++ ++ − −	7
		2/V. 15/V. 23/V.	
11	+++	+++ ++ −	3
		23/IV. 6/V. 15/V.	
12		+++ − −	2
		3/IV. 12/IV. 18/IV. 7/V. 15/V. 18/V. 23/V.	
31		+++ +++ ++ ++ ++ ± −	4
		20/IV. 25/IV. 28/IV. 2/V. 7/V. 15/V. 31/V. 12/VI. 18/VI.	
47		+++ ++ ++ + ++ ± − − −	4
		23/V. 28/V. 2/VI. 7/VI. 12/VI.	
38	++	++ ++ − − −	1½
		3/V. 20/V.	
19	+	+ −	2
		25/V. 28/V. 2/VI. 7/VI.	
42		+ + ± −	2
		25/V. 28/V. 31/V.	
43		± + −	1
		23/V. 28/V. 2/VI. 18/VI.	
48		± ± − −	2

[1] Compare histories in "Dermat. Zeitschrift," l. c.

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After remaining uniform in the beginning, the strength of the reaction generally decreased quite regularly up to the time it became negative. We have never observed any irregular fluctuations between positive and negative, as many observers have reported to be the rule with mercurial treatment.

It was also found that generally speaking, the sera which reacted negatively for some reason or other before the injection, would also remain negative after the treatment. This occurred particularly in cases with primary lesions, but also in some cases of recurrence and malignant syphilis with a negative reaction. On the other hand it was observed—and this has also been confirmed by many others—that in a number of tertiary cases with a negative reaction the latter changed to positive subsequent to the injection.

Five cases of tertiary syphilis in which the reaction was negative preceding the injection, gradually increased in all of them some time thereafter, in some cases up to the degree of complete inhibition. Subsequently during a sufficiently long period of observation, there was a decrease towards a negative reaction in a curve quite as regular.

CASE 1.—Mrs. J. History not corroborative of syphilis. The entire tongue has been transformed into a large, immovable, ulcerated tumour; on its right edge near the apex, two deep crater-like ulcers are seen. The unusually large and indurated glandular swellings in the submaxillary, cervical and sacral regions, suggest the presence of a carcinoma. Microscopic examination of a section however, showed the existence of gummatous tissue and the Wassermann reaction was negative. After 0.45 gm. salvarsan had been injected, the reaction remained negative for a week and a half, became slightly positive (+) at the end of two weeks, then (++) and decreased again to (+), when three and a half weeks after the injection, the woman died of bronchial pneumonia. In the meantime the tongue had almost completely healed. A few days after the injection, the rigid immobility of the tongue ceased and the woman was enabled to masticate and swallow more readily. At the post-mortem examination, only traces of the location of the deep ulcerations were visible. However, the microscopic examination made by Dr. Proskauer showed that the gummatous changes, particularly those in the blood-vessels had not yet disappeared.

CASE 2.—A similar observation relates to Miss D., having two large gummata, one of which covered the left inguinal region in the form of a deep ulcer, with suppurating sinuses the size of a silver dollar, while the second one as large as a hand, was situated below the left scapula. The latter had the form of a deep sac, the largest part of its surface being covered with a partly gangrenous skin-flap which had remained in some places like tissue-bridges. After the injection, the skin-flap was gradually torn into shreds which were carried away

by the active suppuration. At present, the surface of the ulceration slightly reduced, shows perfectly clean granulations. The patient had been treated with iodide of potassium and mercury in every form for several months, without any change whatever in her condition. When she was received at the hospital and while under observation for months, the Wassermann reaction was continually negative. On May 26, 1910, an injection of 0.45 gm. salvarsan was administered. On June 28th, the reaction became slightly positive, constantly increased in strength up to the early part of August and now it is almost completely inhibited.

CASE 3.—Miss S. Infection five years ago; courses of inunctions and injections administered several times; last course of inunctions two years ago for what seems to have been a pustular eruption, scars of which are seen all over the body. At present, the patient comes to the hospital to be treated for a number of ulcerated gummata. In both scapular regions scars with serpiginous edges are present, with evidences of intact bridges of skin as large as the back of the hand. Both scars are surrounded by a circle of ulcerated gummata the size of cherries. Before an injection of 0.45 gm. salvarsan had been administered, on July 19th and once after that date, the Wassermann reaction was negative; then a positive reaction of moderate strength was found twice and three weeks after the injection the reaction was negative again. The gummata healed completely about fourteen days after the injection.

CASE 4.—Willy D. Was injected on April 13th, with 0.3 gm. salvarsan, for serpiginous ulcerations on the shaft and glans of the penis, having been previously treated with frequent courses of mercury for years. Although there was a considerable gain at first, the ulcerations failed to improve sufficiently. A second injection of 0.4 gm. salvarsan was administered on June 27th. Here too, the negative reaction which remained so for some time after the injection became strongly positive two months later. After the second it became less so and ultimately returned to negative (see page 21).

CASE 5.—Flora S. This was a case of serpiginous ulcerations in the anal region, with rectal syphilis. During the months in which the patient was under observation she always gave a negative reaction. Considerable treatment with mercury and iodide of potassium having produced hardly any improvement, 0.3 gm. salvarsan was injected on May 4th. At repeated examinations the reaction remained negative for six weeks until June 17th, but on July 5th the strength of the reaction had changed to (+ + +). On July 28th, the reaction was again negative, having previously shown all degrees of gradual decrease. Repeated examinations made since that time always showed a negative reaction (see page 23).

All of these patients were very decrepit and four of them, the women, were suffering from progressive phthisis. These extraordinary phenomena could hardly be attributed to the preceding treatment with mercury and

iodide of potassium, as in the case of Mrs. J., no specific treatment had been given previously, though the other cases had all been treated with liberal doses of mercury.

I have explained these phenomena in this way. The spirochetes are disintegrated by the injection and thus the substances necessary for the manifestation of the Wassermann reaction find their way into the blood. In this manner we are offered a new method of discovering a veiled Wassermann reaction, which as I have already demonstrated in other cases, is caused by the blocking of the amboceptor by means of complementoids. According to Ehrlich, isolated spirochetes which are no longer capable of producing a biological reaction, are destroyed *en bloc* by the injection. In this manner the total amount of the spirochetal poison is mobilized and the seemingly new appearance of the Wassermann reaction is effected.

Lange then reported additional investigations as follows (*Berliner Klin. Wochenschrift*, 1910, No. 36):

In a total of 268 cases treated with salvarsan, the following results were found in regard to the Wassermann reaction: 153 cases with positive reaction became negative in about four to five weeks; in every case it was evident that the time required to change the reaction to negative depended on the initial strength of the reaction. We would add that we considered the reaction negative when hemolysis was complete. Several days preceding this result, in almost every case we found a reaction of ± with minimal turbidity, proving that the strength of the reaction continually decreases until it reaches zero. Eighteen cases were negative preceding the treatment. Among these was one case of malignant syphilis and one of tabes and both remained negative. Nine cases treated with mercury before the injection of salvarsan always reacted negatively. Two cases of primary lesion, which had been injected while the Wassermann reaction was negative remained negative. The five cases of tertiary syphilis mentioned, became positive after the injection; of these two became negative again, one died with a positive reaction and two cases still show a positive reaction at the present time. After the Wassermann reaction had become negative, its reappearance as positive was observed in two cases, one of which was rendered negative again by a second injection. The second case showed at least a decrease of the strength of the reaction. Ninety-seven cases remained positive, of which fifty-four were unchanged at a maximum period of observation of three weeks. In thirty-four cases there was a distinct decrease in the strength of the reaction during a maximum period of observation lasting five weeks. In only one case, namely severe syphilis of the larynx

which receded very slowly in a clinical sense, there was a continued reaction of (+++), although two injections of salvarsan had been administered; this case was under observation for six weeks.

Since that time the following cases were more carefully controlled:

Cases (reactions) rendered negative:

Primary syphilis, one case in three weeks.

Secondary syphilis, six cases in one week; twelve cases in two weeks; twelve cases in three weeks; seven cases in four weeks; three cases in five weeks.

Tertiary syphilis, one case in three weeks.

The reaction was diminished during an insufficient period of time:

In two cases after one week; in ten cases after two weeks; in one case after three weeks; in three cases after four weeks; in one case after nine weeks.

The reaction remained unchanged:

In seventeen cases after one week; in twenty cases after two weeks; in twelve cases after three weeks; in six cases after four weeks; in three cases after five weeks; in two cases after six weeks; in one case after three months.

One case of malignant syphilis remained permanently negative for six months. One case became positive without clinical symptoms after a negative result.

Of primary cases which were negative before the injection one case became positive after eight days, another after six weeks.

Two cases of tertiary syphilis, which were negative before and became positive after the injection, became negative again after a second injection, and have remained so for three months.

We are therefore unable to say positively at the present moment, whether a permanent negative Wassermann reaction will be obtained in a larger proportion of cases treated with salvarsan than in cases that were treated with mercury.

Toxicity.—Regarding the toxic properties of the remedy, it was found when first introduced, that monkeys could be given 0.15 to 0.2 gm. per kilo of their body-weight. Experience has also shown that therapeutically effective doses have rarely been dangerous in man. In all of my fourteen hundred cases, I have never observed any symptoms indicating essential arsenic poisoning; and even in those cases where death occurred after many days or weeks from other causes, post-mortem examination has never shown

any degeneration of the organs that could be attributed to arsenic poisoning. Nor has any death from arsenic intoxication been recorded by others. In the beginning, I injected 0.45, 0.5, 0.6, or 0.7 gm., first intramuscularly and later subcutaneously. However even considerably larger doses, as administered by Fraenkel and Grouven, i.e., 0.9 to 1.0 gm. sometimes repeated, have failed to produce a toxic effect. Whether or not such symptoms as chills, vomiting and headache, which occasionally follow the intravenous method of injection, may be considered as having been produced by arsenic is very doubtful, as they do not correspond with the symptom-complex seen in cases of poisoning by inorganic or organic preparations of arsenic. For this reason, Ehrlich has justly pronounced the fatal case recorded by Fraenkel and Grouven as not having been due to arsenic poisoning.

"This was the case of a waiter, aged twenty-five, who undoubtedly of syphilitic origin, was suffering from grave disturbances of speech, auditory aphasia, etc., for years. He had a positive syphilitic history and had been treated at the local psychiatric clinic for about a year and a half. The examination of his blood showed a vigourous Wassermann reaction, designated on our charts as + + + +. On August 5th, 0.4 gm. of the remedy, dissolved in 15 c.c. of water, was injected into the veins of the left elbow. The injection was given strictly according to rule; but when the case resulted fatally, I (F.) reproached myself for not having increased the volume of the solution to 150 or 200 c.c., as is usually done and recommended by others, instead of employing the lesser dilution above mentioned. Fifteen minutes after the injection, symptoms of violent arsenic poisoning appeared, i.e., nausea and vomiting and violent abdominal pains; two hours later, a weak pulse which could not be improved even with repeated injections of camphor. About three and a half hours after the injection death ensued. The post-mortem examination revealed several extensive areas of softening in the left temporal lobe of the cerebrum. Further post-mortem examination to ascertain the presence of arsenic, showed that the spleen, lungs, and liver contained a considerable quantity of that substance. Other portions were not examined.

"As the preparation used was properly prepared and as three other patients had been given an intramuscular injection with the identical solution without any untoward symptoms being observed, the fatal result in this case can only be explained as having been the result of an unusual idiosyncrasy of the patient to arsenic, which although very rare, should always be thought of when such a remedy as this is to be introduced into the blood circulation. At any rate, we have ceased giving the intravenous

injections and we believe that the overwhelming majority of physicians will pursue the same course and refrain from introducing the remedy directly into the circulation."

Ehrlich to the contrary notwithstanding, has pointed out the fact that the intravenous method of administration used in many hundreds of cases has not resulted in any injury, and that the patient above mentioned belonged to a group of patients whose central nervous system show extensive degenerative processes; that such persons are particularly endangered by the introduction of the remedy in any form; and consequently should be excluded from this treatment. Another case resulting fatally is reported by Spiethoff (*Münchener medizinische Wochenschrift*, 1910, No. 53, page 1824). He says:

"The course of one case was unfavourable. This was in an undernourished, anemic female patient, aged twenty-eight, suffering from tertiary syphilis of the throat. Three years previously she had undergone a course of treatment with atoxyl. On June 26th, I injected 0.5 gm. of the monacid solution. At that time dangerous complications of salvarsan had not yet been observed and larger doses were generally being given. The injection was administered during the afternoon. Until ten o'clock that evening the patient showed no unusual symptoms. She received 0.01 gm. of morphine subcutaneously and was found dead the following morning at five o'clock, without the other patients in the ward being aware of her death. Autopsy showed (Professor Dürck): Tertiary throat syphilis, with a high degree stricture of the throat; cicatrized gummata of the liver; hypoplasia of heart and aorta. There were no symptoms of any kind indicative of arsenic toxemia.

"Professor Ehrlich believed that death resulted from shock due to pain at the site of the injection, associated with a toxic amount of the preparation. Unfortunately this woman suffered from a number of complications—poorly nourished, interference with respiration and hypoplasia of the heart. Naturally after this experience, I refrained from giving such large doses to cachectic patients and I now believe that similar occurrences can be prevented."

Braendle and Clingenstein report the following (*Med. Klinik*, 1910, No. 34):

The patient was a feeble woman, twenty-eight years of age, with tertiary syphilis of the throat. She was given 0.5 gm. of the monacid solution and on the following night death ensued. At autopsy no lesions referable to arsenic poisoning could be demonstrated. The principal findings at the autopsy were cicatrized gummata of the liver and hypoplasia of the heart and aorta.

A patient of Ehlers died within five days with symptoms of cardiac paralysis (*Münchener medizinische Wochenschrift*, 1910, No. 42, page 2183):

B., aged forty. Was treated eleven years for syphilis without effect. Four years ago, consulted Dr. J. because of girdle pains in the lower thorax and pains in the tibiæ. The latter disappeared after twenty inunctions of grey ointment, 3 gm. each, and potassium iodide. He was advised to take repeated courses of treatment, which he neglected doing in spite of the warnings. In April 1908, he had an apoplectiform seizure. In August 1908, the first symptoms of dementia paralytica appeared. He was taken to the St. Hans Insane Asylum of Copenhagen, but half a year later was returned to his home improved. The attacks disappeared. He was able to be about in his place of business, could ship his goods and had his accounts well under control. In the middle of July 1910, he had another apoplectiform seizure and from that time on he began to fail. Nevertheless, even before he received the treatment with salvarsan he was able to do some gardening, took short walks, read the newspapers and was able to comprehend much of what he read. On August 25, 1910, he received 0.5 gm. of salvarsan subcutaneously in the scapular region. This was absolutely painless and without local reaction. Increasing symptoms of poisoning, exclusively relating to the nervous system—tremour, shuddering, sweating crises, loss of strength, etc. No symptoms pertaining to the organs of digestion. He died five days after the injection, with all the indications of a rapidly progressing cardiac paralysis. Maximum temperature, 104° F.

Autopsy revealed nothing but an acute parenchymatous degeneration of the organs, as the cause of death.

Slighter symptoms which might be ascribed to arsenic poisoning, occur occasionally, e.g., gastric irritation and nausea. In one case where vomiting occurred, Professor Lockemann found traces of arsenic in the vomitus to the extent of $\frac{120}{1000}$ of a milligram in 280 c.c. of vomited fluid. It is interesting to note that in tabetics, obstipation frequently sets in, resembling slight intestinal obstruction and lasting three to four days; this has always disappeared without resulting in injury. It may be assumed that the well-known paralyzing effect of arsenic upon the contractile elements of the mesenteric vessels is particularly active in these cases. Spiethoff has reported an epileptic seizure as an early symptom of intoxication after injection (*Münchener medizinische Wochenschrift*, No. 35, page 1823):

This patient was a powerful man, aged thirty-one, with latent secondary syphilis. He was sent to us from the psychiatric clinic, with the diagnosis of "stupor and latent syphilis." The Wassermann reaction being still positive, he

was given 0.3 gm. of salvarsan in monacid solution. Four hours later, he was seized with convulsions associated with loss of pupil reflex and exaggerated patellar reflex; involuntary micturition followed the convulsions. The patient was not aware of the attack, nor could he remember ever having had any. His parents also stated that the patient had never suffered from epilepsy, although similar psychic disturbances had occurred in his fourteenth year. In the years following, no psychic phenomena were observed until two years ago when he became strikingly quiet and shy. The interesting feature of this case is the reaction of the drug in the cerebrum—the *locus minoris resistentiæ* of the patient. The solution was prepared with methyl alcohol; it therefore remained to be determined whether the cerebral irritation was due to the alcohol or the salvarsan.

A communication from Professor Kreibich's dermatological clinic at Prague caused considerable alarm (Bohăc and Sobotka, *Wiener klinische Wochenschrift*, 1910, No. 30). In fourteen cases these writers observed: 1. Retention of urine in three cases, varying in duration from half a day to ten days; considerable difficulty in urinating still existed after the condition was relieved; in two cases also a trace of albumin was found in the urine. 2. In all of these cases there was a loss of the patellar reflex. 3. In two cases there was a very distinct rectal tenesmus.

In 1,400 cases I have been unable to confirm these observations. A special examination of the patellar reflex in one hundred cases did not show its disappearance in a single instance. Basing his opinion on the reports of Alt, Finger, Neisser, Dörr and Michaelis, who had been using the very same preparation, Ehrlich immediately replied that these injuries were not caused by the remedy and also noted the fact that a loss of the patellar reflex had never been observed by these authors. The symptoms were probably those of poisoning caused by impure methyl alcohol. Bohăc and Sobotka subsequently stated (*Wiener klinische Wochenschrift*, August 4, 1910), that micturition had become normal and the patellar reflex had reappeared and they no longer attributed the injuries to the remedy, although they objected to the explanation of methyl alcohol having caused the toxic symptoms.

Complications, Local and General Hypersensitiveness (Idiosyncrasy).—Still in some cases, local and general complications of a remarkable nature have occurred. In a usual and normal case, more or less edematous swelling or none at all may occur, which at all events, subsequently hardens and becomes callous. In some cases knotty formations result which subsequently melt away in two to four weeks.

Abscess.—I do not now believe, as I at first supposed, that these

symptoms indicate the presence of infection, because the light brownish fluid forming the mass is absolutely aseptic and the entire process of infiltration and softening occurs without fever, a simple puncture being quite sufficient for healing. It is rather to be assumed that salvarsan like most other arsenic compounds, produces a local chemical irritation not unlike a caustic and that the susceptibility to the remedy varies greatly in different individuals. Thus we have prepared ten doses simultaneously and injected them into ten patients with an exactly similar technique and we have seen widely differing effects in this regard.

During the first few days an infiltrate sometimes appears, the size of a closed fist, very red and more or less painful; this mass projects above the level of the skin and at the site of the injection a small, brownish, necrotic eschar may be observed. But frequently these pathologic changes make their first appearance during the second week or even later, or they may be intensified in character and for the first time attain noteworthy proportions during that period.

Necrosis.—Occasionally necrosis develops at the site of the injection. A defect about the size of a five-cent piece can be observed. The skin is brownish-black in colour, very dry and somewhat depressed. However it is not loosened, but firmly adherent to the superficial fascia which has assumed a peculiar pale, light greenish-yellow colour. For weeks the necrotic area remains in this condition, which is not unlike the crust left after treatment with arsenic paste, while the infiltrate is gradually being absorbed. When an incision is made, it is observed that small deposits of salvarsan which are also present in the abscess fluid, remain unabsorbed. It is also seen that the infiltration is very deep and that the margins of the greenish-yellow areas can only be reached when extensive incisions are made. After a long time these conditions return spontaneously to the normal in great measure. Expectant treatment is fully indicated, as these necrobioses are absolutely painless and aseptic and run their course without any secretion, so that they cause little or no inconvenience to the patient. It is sufficient to cover them with sterile gauze. At Königsberg, Orth demonstrated slide preparations of these necroses and emphasized their sterile character. He also stated that there was no suppuration present but only a few peripheral leucocytes. Apart from the varying sensibility of the tissues, which is not dependent on the patient's condition, the technique of the administration of the new remedy plays an important rôle in the development of these necroses. It appears to be essential that either the subcutaneous or the intramuscular method be employed.

General Hypersensitiveness. Exanthemata and Enanthemata.—In addition to the hypersensitiveness of the tissues seen in some individuals, we also observe now and then, idiosyncrasies of a general nature. It is also a fact that these phenomena are uncommonly frequent just in those patients that give evidence of an idiosyncrasy of the tissues. Such cases I have already described.

On July 3d, I injected three paralytics intragluteally at the clinic of Arndt and Nawratzky. On July 10th and 11th, one of them became violently feverish; and at the site of the injection a reddening of the size of a man's palm appeared (see Figs. 1 and 2, page 61). The fever continued on the following day and simultaneously, a generalized morbillous exanthem associated with conjunctivitis appeared. The pulse was good and the general condition did not appear to be alarming. The urine was free from blood and albumin. I believed I was dealing with an arsenic exanthem, but I abandoned this view when subsequently the other two patients also manifested similar symptoms and all of them rapidly recovered. Arsenic exanthemata are accompanied by changes in the parenchymatous organs followed by prolonged vital depression, even in favourable cases. When I was advised that in the second patient a similar complex of symptoms had also appeared, I believed that although the parts had been made sterile with iodine, I had to deal with an infection of one patient by another through pathogenic skin bacteria, which these unclean paralytics were carrying on their persons in spite of the disinfection.

Since then, I have seen a larger series of similar exanthemata and they have also occasionally been described by others. It has been observed that quite a typical picture makes itself manifest. Almost always a reddening the size of a man's palm, is formed at the site of the injection on the seventh to the tenth day. Generally a small eschar is also developed at the site of the injection; likewise small, flat pustular blebs on the erythematous spot, which in some parts show a depression and resemble an arsenical herpes, as shown in Plate XVI. At the same time, the temperature which has been normal thus far, rises to 105.5° F., and an eruption appears. Generally it is of a morbillous character, but sometimes is diffusely erythematous or scarlatiniform (sprouting). The conjunctivæ are also involved. The eruption generally appears at some distance from the original erythematous spot on the trunk and extremities, preferably upon the extensor surfaces and it is conspicuously symmetrical. This condition is accompanied by gastric symptoms—diarrhœa, excessive thirst, heavily coated tongue and occasionally, vomiting. The patients feel very miser-

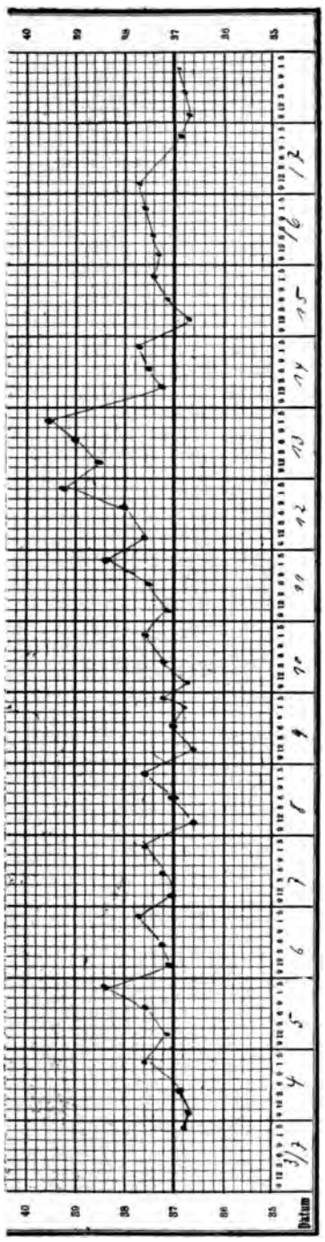


FIG. 1.

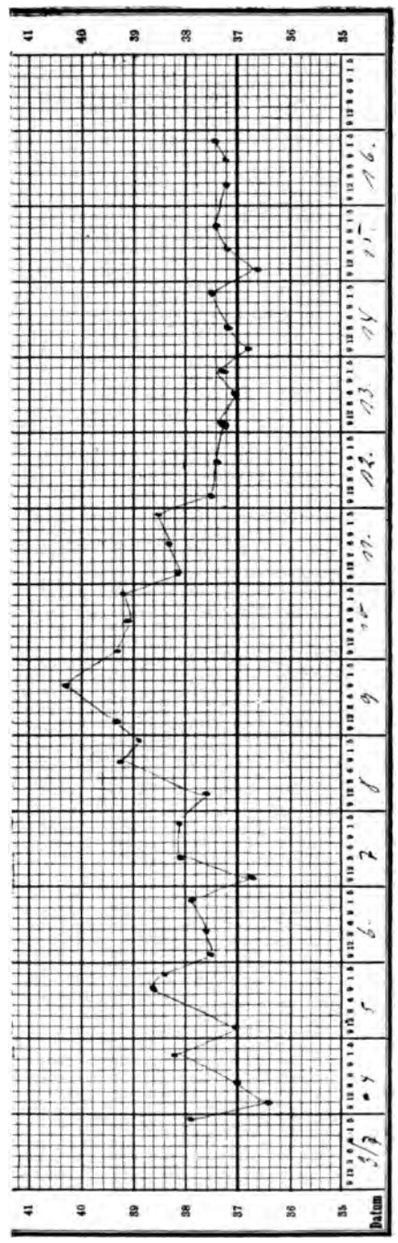


FIG. 2.

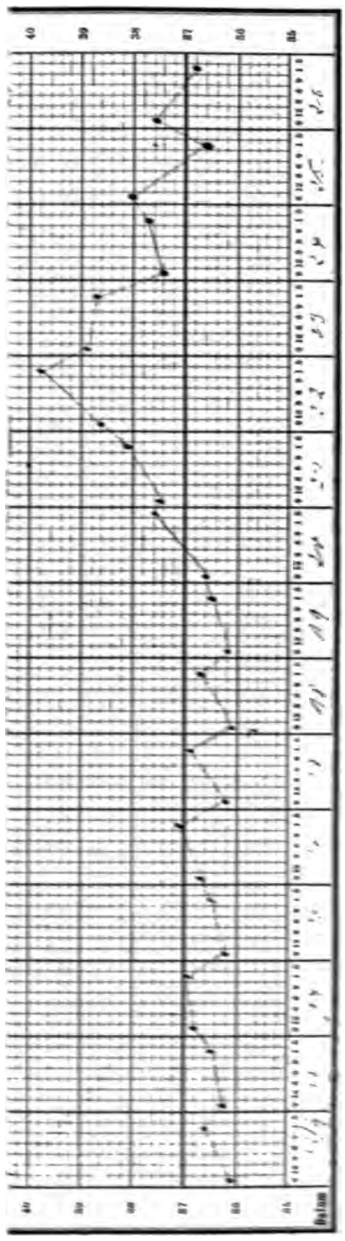


FIG. 3.

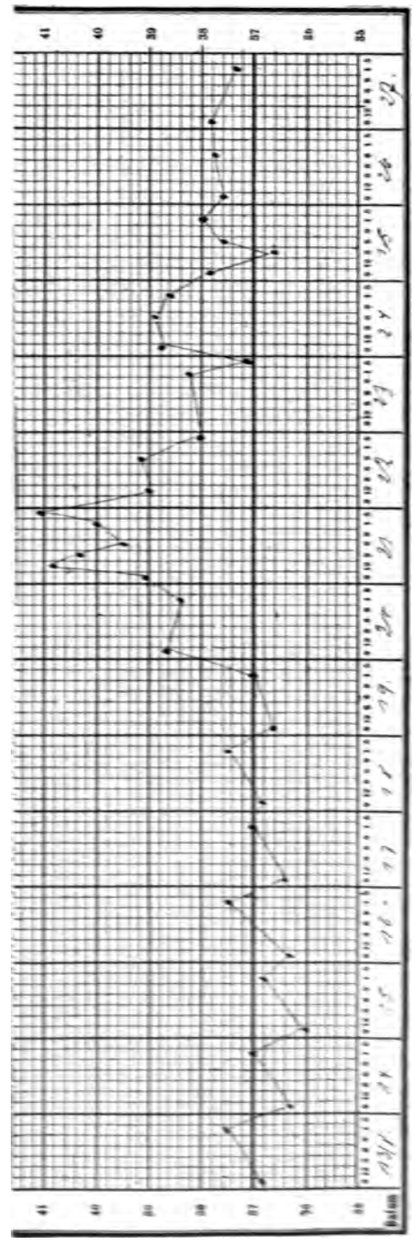


FIG. 4.

able, but their pulse generally remains good. We never found albumin or sugar in the urine. However, slighter abortive forms also occur.

Still more alarming are the cases in which high fever appears after eight to ten days, without the development of exanthemata. In these cases we always have an angina with streptococcus infection or with erosions on the palatoglossal arch. My original supposition that here we had to deal with infectious diseases (angina, coryza), taking a peculiar course owing to the action of the remedy, cannot be maintained, as I believe that these cases should rather be taken as enanthemata; it is also quite possible that they may also be found upon the mucous membrane of the stomach and intestines. The following may be mentioned as a typical case (see Fig. 5):

On July 4th, G., suffering from bone syphilis, was given an intragluteal injection. The first two days were passed very satisfactorily; on the five following days, the temperature rose to 100.5° F. in the evening and there was great pain in the leg. On the morning of July 11th, the temperature was 98.6°, and in the evening it was 102.2°; on the 12th, it was 98.6° in the morning and 104° in the evening, and on the 13th it ranged between 104° and 106° F. At the same time the pulse was very rapid and small but regular. The patient was very thirsty and for a time unable to urinate, though the catheter was not necessary. Although the symptoms were not typical, I thought of arsenic poisoning in spite of the fact that the urine did not contain albumin or blood. I also thought it would be necessary to make an incision at the site of injection for the purpose of removing the deposit. But during the day the patient began to perspire vigourously, the pulse became better and his general condition improved. On July 14th, the temperature fell from 105° to 103°; on July 15th, 99.5°, while it rose again to 103.7° during the evening, and then it fell to the normal. On July 14th, a lacunar angina was positively diagnosed and on July 15th, flat erosions on both of the palatoglossal arches appeared, all of which healed quite rapidly. Within two or three days the patient had recovered completely, so that he was discharged feeling perfectly well. He has since then remained well. On the ninth day, Professor Lockemann found only traces of arsenic in the patient's urine, the amount corresponding to the normal excretion, $\frac{8}{1000}$ milligram in 125 c.c.

Another case was that of a young physician, who from his youth had suffered from a low-grade nephritis. On July 29th, he was given 0.5 gm. of salvarsan subcutaneously for syphilitic periostitis of the tibia. In the beginning his case progressed favourably, but on August 7th he suddenly developed high fever and angina (see Fig. 6). At the same time

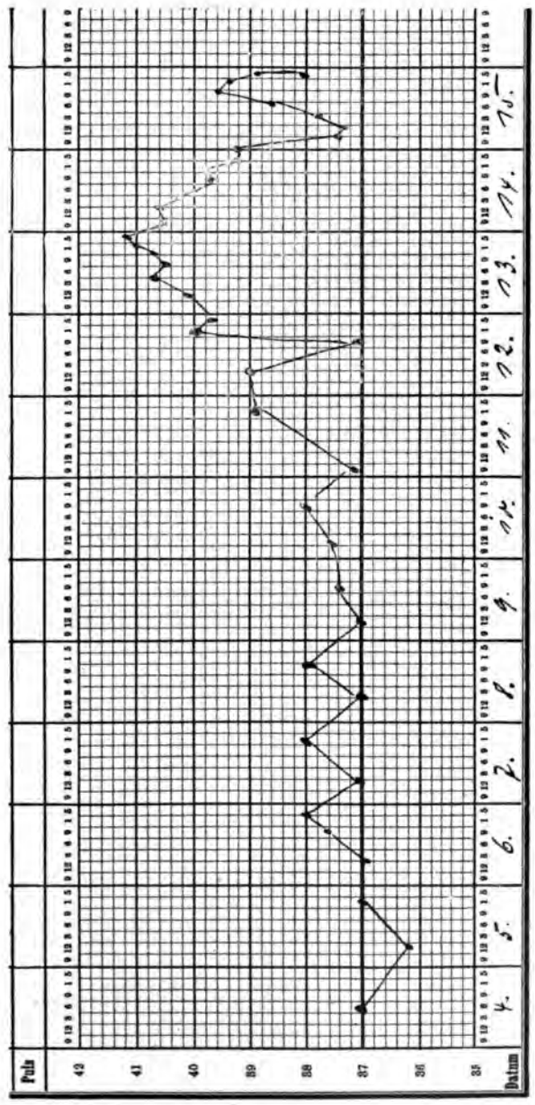


FIG. 5.

his nephritis became strongly hemorrhagic. The microscope showed numerous red blood corpuscles and casts. The pulse was very rapid but good; the behaviour of the pulse in these apparently alarming cases is a safer criterion than the temperature. The latter fell to normal in two days and the nephritis returned to its usual level a few days later. A similar case with angina and slight albuminuria is illustrated in Fig. 7, page 66. Mrs. B. presented quite a different type, as illustrated in Fig. 8, page 66.

One who has frequently observed these exanthemata and enanthemata—and they occur in about one per cent. of the cases—cannot doubt in the least

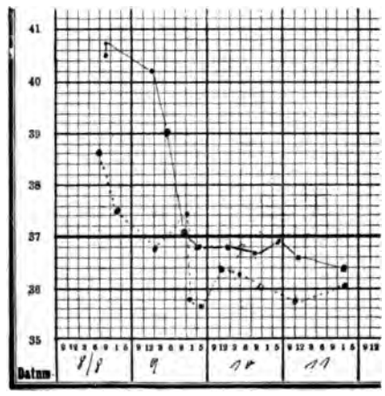


FIG. 6.

that here we have to deal with a typical pathologic picture. It is really striking that in these cases an incubation period of eight to ten days precedes these phenomena. The grave symptoms consequently only arise when the principal mass of the substance introduced has already been eliminated or enclosed in a tough wall of inflammatory tissue, as the result of which only very small quantities can possibly be absorbed. But we have an exact analogy to these processes in the serum disease, as described by von Pirquet and Schick (Vienna, 1905, Deuticke). Here also, rather similar phenomena do not make their appearance until the eighth to the tenth day after the introduction of the serum, which is surely no longer present in the body as such. These authors have also demonstrated that the serum as such does not exert a toxic effect, but that the toxic body develops only through the reciprocal effect between organism and antigen.

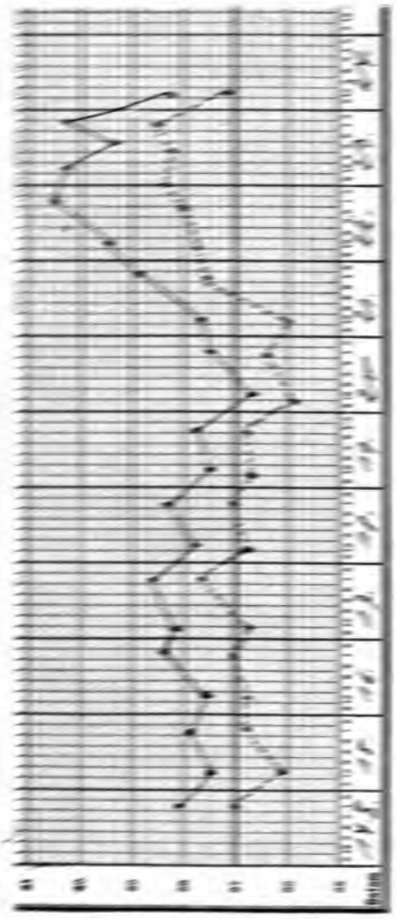


FIG. 7.

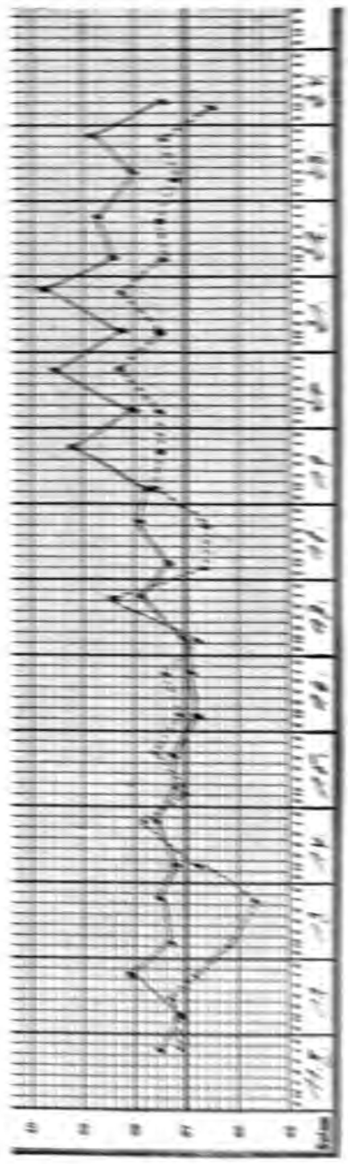


FIG. 8.

Jarisch-Herxheimer Reaction.—In this connection it is well to understand the Jarisch-Herxheimer reaction which appears more frequently and vigourously after the use of salvarsan than with mercury. Gennerich also shares the opinion that this reaction is produced by the liberation of endotoxines. Resembling in great measure the course of the disease, the latter are capable of producing a more or less visible local tissue-reaction, analogous with the positive Wassermann reaction provoked by the injection of salvarsan. As the result of my own extensive observations as well as the numerous contributions to the literature—Gennerich has seen this reaction quite regularly—we can no longer assume that the reaction is due to an extremely inadequate dosage. As a matter of fact, in cases in which this reaction is present, the symptoms seemed to disappear more promptly than otherwise.

It should also be ascertained whether or not there exists a "hyperenergetic" reaction, particularly in cases where some of the remedy is being inoculated into the skin. At least we might in this manner account for the local reddening and swelling, the formation of necrosis at the point of injection and the suppurating vesicles in their adjacent vicinity, because of their analogy to the symptoms of vaccination, as described by von Pirquet (Allergie: "Klinische Studien über Vaccination und vaccinale Allergie," Vienna, Deuticke). On the other hand, I have not observed any local hypersensitiveness, nor any increased general reaction after reinjections have been administered. In only one instance the first injection was well tolerated, but the second was followed by the formation of abscess. However, these conditions still require a much more thorough research, particularly in regard to the question whether or not the hypersensitiveness observed after the first injection will assume a more dangerous character after a second. I have not yet had an opportunity to reinject in such cases; but if I had, I would first try to determine the degree of hypersensitiveness by means of a cuti-reaction.

Reinjection.—It seems most unwise to select the eighth to the tenth day for reinjection, this being the most critical period when the reaction of the organism is at its maximum. This is also very well demonstrated by a case of Gennerich's, in which 0.55 gm. was well tolerated, but a second injection nine days later gave evidences of hypersensitiveness. The case was the following:

K., able seaman, infected early in June 1910. Hard chancre. August 8th, alopecia and roseola. Two injections of calomel. August 17th, the chan-

cre and the eruption still present; 0.55 gm. salvarsan. Moderate pain lasting about six hours. During the night, restless and uncomfortably warm. August 18th, the eruption disappeared. August 19th, the chancre entirely healed. August 26th, no pathologic symptoms present. Owing to the persistence of the positive serum reaction, 0.3 gm. salvarsan was injected. There was no pain after this injection. In the evening the temperature began to rise. August 27th, general malaise, fever up to 105° F., pulse very small and weak. August 28th, gradual fall in temperature; feeling better; tolerably good appetite. Camphor continually for the pulse. August 31st, general condition satisfactory; slight weakness; appetite and heart action good; appearance of a macular (arsenic ?) eruption on entire body. September 1st, eruption no longer present; general condition excellent; everything normal.

SERUM REACTION

August 9th +	August 21st +	August 27th +
" 13th +	" 22d +	" 29th +
" 17th +	" 23d +	" 30th −
" 18th +	" 24th +	September 1st −
" 19th +	" 25th +	" 2d −
" 20th +	" 26th + (weak)	" 3d −

On account of the general distrust which prevailed until recently in regard to arsenical preparations, the introduction of Ehrlich's salvarsan into medical practice met with the principal objection that its repeated administration in small doses was dreaded because it was feared that symptoms of hypersensitiveness might thereby develop. The very same fear also prevailed in regard to repeating larger doses; because according to analogy with experimental studies in trypanosoma, the immunization of the spirochetes to the remedy had to be taken into consideration. Experience however, has not altogether set aside these doubts, though they have been curtailed considerably.

Our first cases of newly born infants with hereditary syphilis and afflicted with pemphigus, and in all probability destined to result fatally, demonstrated that in some cases certain pathologic symptoms appeared after the injection of 0.03 gm.; the supposition was natural that intoxication had been caused by the decomposition of large masses of spirochetes in the internal organs, which were saturated with the products of syphilis. We then reduced our doses to 0.015 to 0.02 gm. in these cases, repeating them in about eight to twelve days.

According to this method we have treated a considerable number of

syphilitic infants, with the result that the symptoms disappeared without any injurious after-effects. We were thus encouraged to administer a second and stronger injection in those cases of grave malignant syphilis previously described (cases of Willy D. and Flora S.) with the most splendid result. In these cases some very insignificant ulcerations remained uncured, probably because the dose injected was not sufficiently large. The second injection with a larger dose, was given at a time when at all accounts, the elimination of the first dose should have been completed.

A large number of observations shows that the dangers of hypersensitiveness and of the spirochetes becoming salvarsan-fast, cannot be very serious. The objections in regard to the second item are not particularly important, as the remaining spirochetes have not in all probability come into contact with the remedy (compare my paper entitled "Ueber Reinjectionen von Dioxydiamidoarsenobenzol," *Deutsche medizinische Wochenschrift*, 1910, No. 37).

There is but little danger that intoxication might be caused by the cumulative effects of repeated injections, inasmuch as the absorption from the dense infiltration is not very great, this being shown by the constant elimination of only small amounts of arsenic.

CONTRAINDICATIONS.—The number of contraindications has proven to be less than had been at first expected.

Pregnancy.—Pregnant women have tolerated the remedy very well, during all stages of pregnancy. We have thus far treated ten cases. We have not seen any ill effects on the infants, one such case having been observed by Glück. The movements of the child were not interfered with and the fœtal heart-sounds were distinct. Normal delivery occurred in three instances.

Case 1.—Mrs. P., on July 5th, 0.45 gm. neutral emulsion.

August 4th, Wassermann reaction, + + +. September 9th, Wassermann reaction, −. Delivery on August 11th (seven months). Infant without any symptoms. Wassermann reaction, −.

Case 2.—Mrs. K., on July 26th, 0.45 gm., neutral emulsion. July 23d, Wassermann reaction, + + + +. August 2d, Wassermann reaction, + + +. August 9th, Wassermann reaction, + +. September 26th, Wassermann reaction, −. Delivery on September 11th. Infant vigourous, one pemphigus vesicle (specific ?) on the back of the left hand. Wassermann reaction, +.

Case 3.—Mrs. S., on July 28th, 0.45 gm., neutral emulsion. July 27th, Wassermann reaction, + + +. August 9th, Wassermann reaction, + +. Delivery on September 28th. Infant has scaly eruption on hands and feet. Wassermann reaction, +.

Consequently in only one case we observed an effect on the fœtus that might have been considered as curative. However even this one case is doubtful, as the freedom from symptoms in the beginning does not, *per se*, prove the absence of syphilis, while on the other hand healthy children may also be born of syphilitic mothers.

Tuberculosis.—The remedy is very well tolerated by tuberculous persons in all stages, a very important fact when we consider the deleterious effect of mercury in the joint presence of severe tuberculosis and syphilis.

Nephritis.—Nephritics may also be treated without injury to their kidneys. In those cases in which the difficult question arises, whether or not a nephritis is of syphilitic nature and when a doubt exists as to the usefulness of mercurial treatment, the advantage possessed by the new remedy is very great, in view of the rapid disappearance from the urine of albumin due to syphilis.

Pernicious Anemia.—We have also administered the remedy to patients greatly debilitated by pernicious anemia, without any betterment of the condition and withal without any injurious secondary effects.[1]

Hemorrhage.—Great caution is required in affections having an inherent tendency towards the development of hemorrhage, as arsenic exerts a toxic effect upon the walls of arterioles and capillaries. In a few cases in which concurrent inflammations had existed at the time of the injection, we observed injuries of that kind. For instance, an otitis media was followed by a hemorrhagic exudate subsequent to the injection and an ordinary nephritis became hemorrhagic temporarily, when symptoms of hypersensitiveness appeared on the tenth day after the treatment. On one occasion we noted a hemorrhage of the pharynx on the second day and a severe hemoptysis in a consumptive forty-eight hours after the injection. In a case of herniotomy, an unusually violent oozing of blood occurred fourteen days after injection.

Heart.—Cardiac weakness and disease should be considered as contraindications. For this reason I requested Professor Nicolai to examine a number of cases treated with salvarsan and his report reads as follows:

'I have examined a considerable number of patients (forty-seven), who were about to be treated with injections of salvarsan, carefully observing the heart action preceding the treatment. The remedy was withheld from those in whom

[1] Klemperer was also not able to record any success with salvarsan as compared with the favourable effect of arsacetin (see H. Lindenberg, "Neuere Versuche in der Behandlung der Perniciösen Anämie," D. J., Berlin, 1910).

serious defects of the heart were found; that is, distinct valvular defects and also marked cardiac insufficiency, dependent upon myocarditic and arteriosclerotic changes. Therefore the treatment was given to only thirty-eight of the patients whom I examined. Of these thirty-eight patients I reexamined twenty-seven after the treatment, once, twice, or even three times, either immediately or a few hours or several days after the injection. In a few instances the examination was made several weeks later. No injurious effect was recorded in any of these patients, none of whom was suffering from serious cardiac disease. Neither in respect of the physical examination (Roentgen rays, blood-pressure test, electro-cardiogram, auscultation), nor of the subjective condition of the patients, that is, in regard to the functional tests of the heart action, was any deleterious result noted. In about one-half of the cases examined, a slight diminution of the electro-cardiogram was observed, generally exceeding the degree observed in every-day life in different examinations of the same person. However in some of the patients an increase was noted, though a very slight one. Therefore in view of the fact that a decrease or an increase of the electro-cardiogram did not necessarily indicate the presence of a stronger or a weaker heart and in view of the limited number of cases examined, I should not attribute any great importance to this fact, particularly as the decrease was not very pronounced in any of the cases. But another fact observed in this connection was not without its significance. Of the thirty-eight patients to whom an injection had been administered, seven patients had an increased blood pressure of fifteen to eighteen c.m. of mercury. Five of these seven patients presented themselves for a second examination after the injection and in four of these five the blood pressure had diminished two or three c.m. of mercury. In the fifth case the blood pressure remained unchanged. These facts may be important inasmuch as syphilitic changes in the aorta are generally accompanied by a high blood pressure; and these observations would seem to indicate that these aortic changes at any rate, do not constitute a contra-indication against the injection of the remedy. But whether the decrease of blood pressure is permanent or not, or simply indicative of a curative process in the basic blood-vessel changes, or whether it is a specific toxic effect of the preparation cannot as yet be determined. Furthermore it should be pointed out that even while serious cases of heart disease were excluded, as mentioned above, some twelve patients were given an injection of salvarsan who had diverse minor heart lesions or an imperfect vascular system. That such a large number came under observation is due to the fact that Wechselmann referred to me only such patients in whom a heart lesion was suspected. But even in the twelve cases with diseased heart, there has been no injurious effect as a result of the injection."

Encouraged by these observations, I treated two cases of dilated aorta, as well as a small aneurism, with doses of 0.3 to 0.1 gm. salvarsan without any injurious effect whatever. I have also successfully administered

an injection of 0.4 gm. salvarsan to a man eighty-five years of age, with markedly sclerotic arteries, who presented a fresh primary lesion on the prepuce and a papular syphilide. I am reluctant about treating patients with a flabby myasthenic heart, such as we often find in tabetics. The same is true in cases of stenosis, as I fear an excessive diminution of the arterial blood pressure similar to that which we find in arsenic poisoning.

However broadly speaking, a weak heart would present a contraindication against the new method, because of the occurrence of hypersensitiveness in isolated cases.

Other Effects of Salvarsan.—Concerning the other effects of the remedy we can say that they are principally of a tonic character, similar to those produced by arsenic in general. The bodily strength frequently increases on the very day of the injection and the patients also often notice an increase of sexual potency. The complexion of the patient invariably takes on a better colour and a considerable gain in weight is not an unusual occurrence. Particularly is this true in patients debilitated by malignant syphilis, in whom the cachexia disappears with surprising rapidity. Such patients often gain from thirty to forty pounds within three or four weeks. It should be remembered that this stimulating effect is in itself an essential factor in the almost magical results observed in this group of diseases. The fact that epithelization is stimulated by the remedy, even in non-syphilitic lesions of the skin, is another of its peculiarities. We observed this phenomenon, for instance, in the granulation of an area the size of a palm, after a phagedenic bubo had been excised, the phagedena in other parts remaining unaffected. A woman with pemphigus presented a defect twice the size of a palm, on the attenuated skin which covered an umbilical hernia as large as an adult's head. Though the pemphigus had healed temporarily, the skin defect resisted all treatment for about a year and I therefore transferred her to the hospital for incurables. Epithelization promptly took place after 0.45 gm. salvarsan had been administered. Though this effect corresponds with that known to be produced by other arsenic preparations, it is far greater with salvarsan than with other forms of the drug.

The satisfactory result in pemphigus also probably depends on the same cause. I once observed an excellent result in a case of pemphigus vulgaris, the same observation having also been made by Fraenkel and Grouven. In a case of pemphigus foliaceus I also noticed an improvement; but in other cases there was no change for the better. In several cases of psoriasis we saw no effect whatever, this being contrary to

Kromayer's experience; neither did we observe any effect in lichen ruber planus.

Injection of the Remedy.—As regards the injection of the remedy into the body, Iversen and Schreiber prefer the intravenous application, but most other authors favour the intramuscular or subcutaneous methods.

Alt has devised the following technique for the latter method:

Ten c.c. of sterile water is deposited by means of a pipette into a low beaker or mortar having a capacity of fifty c.c., the dose of the remedy is added, and the whole stirred with a pestle.

Then a sufficient quantity of sterile normal sodium hydrate solution (four per cent. NaOH) is added, until but a minute part of the substance remains undissolved. Generally from 2 to 2.3 c.c. of the soda solution will be sufficient. To this is added sterile water up to twenty c.c. In some hypersensitive cases a sterile local anesthetic may be added. The skin of the patient having been thoroughly cleansed, as for any surgical operation, ten c.c. of the solution is injected into each of the buttocks, deeply, slowly and gently.

[It is well to stop the piston for one or two seconds at each c.c. mark on the barrel of the syringe and to move the free end of the needle around in various directions. It is also conducive to a painless injection to rub the skin with ether until it is red, just before the injection is made. The needle should be about one and three quarter inches long and of good calibre (No. 19 standard gauge). It goes without saying that the syringe and needle, as well as the mortar and all the other accessories, should be thoroughly boiled and made sterile. The operator's hands should also be cleansed and sterilized.—The Editor.]

The patient should lie face down and remain in this position half an hour. An ampulla of eusemine[1] seems to have been effective as an anesthetic. Unfortunately this injection is frequently rather painful, especially in very sensitive persons; but the pain generally disappears after twelve to twenty-four hours.

Following the advice of Ehrlich, in the beginning I partly dissolved the salvarsan, melted in a vacuum with a small amount of methyl alcohol or glycol, adding about ten c.c. of distilled water, then adding one to two c.c. of one-tenth normal caustic soda. To this is added distilled water up to twenty-five c.c., and this strongly acid solution is injected intragluteally. Subsequently we added one-tenth caustic soda until the solution became

[1] A local anesthetic consisting of cocaine and adrenalin.—[Ed.]

slightly turbid, monochlorhydrate being formed. We have also applied the remedy dissolved in water only, or using less fluid than above mentioned; but there was hardly any appreciable difference in the amount of pain. The injection itself does not necessarily cause much pain; nevertheless by a previous injection of 0.02 gm. of novocain we can render the deepest point of the injection absolutely insensitive. Generally the pain appears after several hours, sometimes even later than that; and it is usually quite severe, a neuralgic piercing pain extending down to the calves being felt for several days and interrupted by almost painless intervals. Some patients however, hardly feel any pain.

The duration of the pain is from one to six days. It is more or less severe and narcotics are sometimes necessary to control it. Simultaneously, the temperature often rises to 100° to 102° F., but not always. Nevertheless in spite of the pain and temperature the patient's condition is quite satisfactory, a phenomenon which is rather surprising. Generally the entire gluteal regions are edematous. Only once, fourteen days after the injection, we observed a small area of softening unaccompanied by pain or fever, which was quickly relieved by a puncture. At the end of a week in most cases, there is still some pain in walking about.

We were much more successful when in June, we gradually reduced the degree of acidity and ultimately employed neutral emulsions. The fear that these emulsions might be less effective than the acid solutions was soon removed after successful experiments with mucous patches, which offered an excellent opportunity for study. We dissolved the preparation as heretofore, added a drop of phenolphthalein solution as an indicator, and then carefully added one-tenth normal caustic soda until a fine yellow powder was precipitated. Twenty-five to thirty c.c. of this slightly acid or neutral solution was injected intramuscularly and subsequently with identical success subcutaneously into the gluteal region. Then Lange observed that salvarsan is soluble in commercial caustic soda. Consequently it was no longer necessary to use methyl alcohol, a substance which, according to observations made by Guth at Professor von Grosz's Eye Clinic at the Budapest University (*Orvosi Hetilap Szemészet Ophthalmologia*, August 29, 1909), produces amaurosis in hypersensitive persons, even when introduced in minute quantities. He also found that the quantity of fluid to be injected could be reduced from four to eight c.c. We then did away with phenolphthalein, this being not altogether neutral, for the solution of salvarsan in caustic soda, to which it gives a purple colour, which in turn is changed to citron-yellow after precipitation of the salt on

the addition of acetic acid, no longer becomes red again on the still further addition of caustic soda. This is probably due to the fact that phenolphthalein is destroyed by the arsenic preparation through the addition of acetic acid, a result not produced by acetic acid alone, nor by the acid solution of salvarsan. Our technique therefore, is as follows (published in the *Deutsche medizinische Wochenschrift*, July 28, 1910, No. 30):

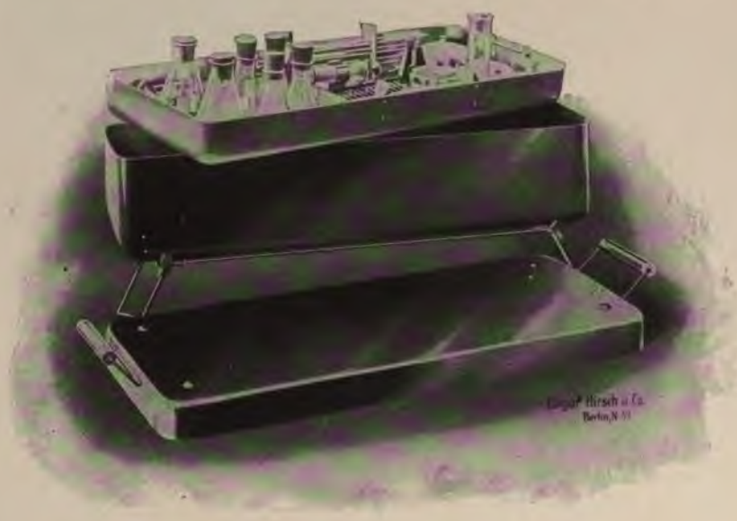
The preparation is placed in a mortar and dissolved after thorough mixing in one or two c.c. of commercial caustic soda; then glacial acetic acid is added, drop by drop, until a fine yellow slimy sediment is precipitated, to which one or two c.c. of sterile distilled water is added. The liquid is now neutralized by the addition of one-tenth normal caustic soda solution or one per cent. acetic acid, according to the reaction shown by litmus paper. Inasmuch as this reaction is obtained with some difficulty in the form of a suspension and as the amount of pain depends on complete neutralization, we centrifuge the emulsion and take up the sediment with a physiologic salt solution. Then the solution is drawn into the syringe and slowly injected subcutaneously under the shoulder blade, after previous disinfection of the skin with tincture of iodine. This injection is usually quite painless. However, a slight swelling may appear on the second or third day (with reference to hyperesthesia, see below), but the temperature rarely rises much above the normal. According to the literature, it appears that most observers have prepared their injection according to this method. I have also had a set of special instruments made by Edgar Hirsch & Co., 19 Lindower Strasse, Berlin, with which the sterile character of the injection is assured (see illustrations, pages 76 and 77).

At about the same time that we were making these researches Leonor Michaelis, altogether independently, made the injection in neutral suspension; but the quantity of fluid injected by him was much larger. (Communicated to the Medizinische Gesellschaft, July 6, 1910, and published in the *Berliner klinische Wochenschrift*, July 25, 1910.) His method is as follows:

From 0.3 to 0.6 gm. of sodium hydrochlorate is dissolved with sixteen c.c. of very hot sterile water in a wide, graduated cylinder having a capacity of fifty c.c. The powder is now added and the whole thoroughly shaken, a thick glass rod assisting in crushing and stirring the powder. When the mass is dissolved, from three to five c.c. of normal caustic soda is added, well stirred, and then three drops of a one-half per cent. alcoholic solution of phenolphthalein are added and triturated back with standard acetic acid until the phenolphthalein is completely dissolved, a fine yellow

suspension being formed. Finally a few drops of caustic soda are added to slightly recolour the phenolphthalein and then the solution is ready for injection. Subsequently Michaelis also reported the results of subcutaneous injections made by him (*Berliner klinische Wochenschrift*, August 15, 1910).

Blaschko (*Berliner klinische Wochenschrift*, 1910, No. 35), in order to obtain a neutral suspension, uses a twenty-per-cent. solution of caustic soda. He employs 0.45 gm. of twenty per cent. by weight sodium hydrate solution (sp. gr. 1.25) which is equivalent to 0.36 c.c. of this solution for 0.5 gm. of the dichlorhydrate of salvarsan. On carefully adding some sterile



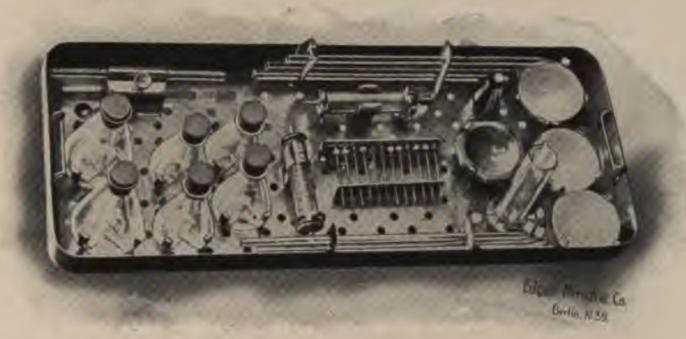
water to the soda solution, we get a neutral mixture, requiring at the most one or two drops of dilute acetic acid; or better still, hydrochloric acid. The mixture is increased up to eight or nine c.c., with the result that a physiologic salt solution of 0.82 to 0.75 per cent. is obtained. An increase to five c.c. is however, also sufficient.

Heinrich Citron and Paul Mulzer describe the following method of preparing the liquid for the injection ("Über die Herstellung Gebrauchsfertiger Lösungen von Dioxydiamidoarsenobenzol, Ehrlich-Hata, 606;" *Medizinische Klinik*, 1910, No. 36):

The determined quantity of salvarsan to be used is emptied from the tube into the barrel of a sterile Record syringe having a capacity of fifteen

c.c. The canula end of the syringe is closed with a tightly fitting cap. The piston is taken out of the barrel. The substance is now moistened by the addition of a few drops of alcohol. Five c.c. of hot water is now added, the piston is reinserted and the clasp-ring adjusted. The whole is well shaken until a gold-yellow solution is obtained. The piston again having been removed, the liquid is shaken slowly and forty drops of a ten-per-cent. mixture of calcium carbonate in physiologic salt solution are added. Thus a thick, creamy emulsion results, which is injected into the gluteal region.

Alt ("Zur Technik der Behandlung mit dem Ehrlich-Hataschen Syphilis-Mittel," *Münchener medizinische Wochenschrift*, 1910, No. 34) rec-



ommends the following alkaline solution: Thirty glass pearls of medium size are placed in a slender glass cylinder having a capacity of one hundred c.c., with a narrow neck and ground glass stopper. Ten c.c. of distilled water is added and then the substance. On shaking the cylinder rapidly and vigourously a clear solution is obtained. Then addition is made of 0.5 c.c. of sodium hydroxide for each 0.1 gm. of the substance and the whole is shaken half a minute. The solution thus obtained may be well diluted with distilled water.

Dr. Richard Volk ("Über eine vereinfachte Injektionsmethode des Ehrlichschen Präparats," *Wiener klinische Wochenschrift*, 1910, No. 35) rubs the powder with liquid paraffine or sterile olive-oil in a quantity of five to eight c.c., and injects this emulsion subcutaneously.

Kromayer ("Eine bequeme, schmerzlose Methode der Ehrlich-Hata-Injektion," *Berliner klinische Wochenschrift*, 1910, No. 37) also recom-

mends the injection of a paraffine emulsion of the preparation. He mixes 3 gm. of salvarsan with liquid paraffine in a mortar, adds up to thirty c.c. of the liquid and thus one c.c. contains 0.1 gm. of salvarsan.

He then proceeds to inject the preparation in doses of 0.1 to 0.2 gm. every day to out-patients; that is, one c.c. of the emulsion ("Ehrlich-Hata 606, in der ambulanten Praxis," *Berliner klinische Wochenschrift*, 1910, No. 39).

Duhot (*Annales de policlinique centrale de Bruxelles*, 21, IX., 1910, and *Münchener medizinische Wochenschrift*, No. 42) dissolves salvarsan in one-half c.c. methyl alcohol, and adds four to six c.c. of physiologic salt solution. This he injects at the junction of the upper and middle thirds of a line drawn from the anterior superior spine to the gluteal fold. This is almost exactly the method we first employed and later discarded.

Taege (same journal, page 2180) adds two drops of glycerine to 0.1 gm. of salvarsan, stirs both together, then dissolves in hot water and injects deeply into the intragluteal muscles.

Iversen dissolves the substance in about 15 c.c. of distilled water, adding normal sodium hydroxide, drop by drop, until the precipitate thus formed is dissolved; he then neutralizes the excess of soda with one per cent. acetic acid (about two c.c. of one-per-cent. solution to 0.3 gm. salvarsan). Then he adds half a litre of physiologic salt solution heated to 104° F., and injects with an infusion apparatus into the median basilic vein.

Schreiber and Hoppe (*Berliner klinische Wochenschrift*, 1910, No. 31) describe the following technique for the intravenous injection: Into a graduated cylinder of two hundred c.c. capacity, ten to twenty c.c. sterilized water are decanted, then 0.3 to 0.6 gm. of the substance and a few drops (0.3 c.c.) of methyl alcohol are added. This is well shaken until a clear solution results. To this solution about one c.c. of normal sodium hydroxide is added for each 0.1 gm. of the substance. An 0.8 per cent. sterilized solution of sodium chloride is decanted in a quantity up to 180 c.c. Shake again until the solution is clear; if not, add a few drops of sodium hydroxide and a sufficient quantity of the sterile salt solution to bring the amount up to 200 c.c.

Recently Schreiber recommended the following (*Münchener medizinische Wochenschrift*, 1910, No. 39):

"Into a graduated cylinder of 250 c.c. capacity, having a ground glass stopper and narrow neck, about ten to twenty c.c. of sterile water are decanted. The substance is now added, 0.3 gm. for females and 0.4 for males, shaking vigourously until a clear solution results. An addition of

methyl alcohol is no longer required, as the preparation is readily soluble in water in its present form. This solution is increased up to one hundred c.c. by the addition of sterile water or physiologic salt solution. About 0.7 c.c. of normal sodium hydroxide is now added for each 0.1 gm. of the substance, shaking vigourously until the precipitate thus formed is completely dissolved; if not, several drops of the normal hydroxide are added very cautiously until a perfectly clear solution results. The solution is now made up to 200 c.c. (of course, 150 c.c. or 250 c.c. may also be chosen instead of 200 c.c.). The solution is best prepared with warm water. It should be decanted into a sterilized glass beaker or mortar from which it may be conveniently drawn into the syringe.

"We are using a syringe and canula manufactured by the firm of B. B. Cassel, Frankfurt-on-the-Main, Hansahaus, Stiftstrasse. The canula is bent in the form of a bayonet and provided with a lateral tube and a three-way cock, so that it is possible to draw in the liquid and then inject it into the vein by simply turning the cock. The canula is also provided with a rectangularly bent plate at the point of the bend, for better support by the operator. At present it is so constructed that it can be unscrewed and readily changed.

"It is very important that the canula should be inserted into the vein very carefully. It should rest completely in the vein without otherwise injuring it. This may happen when the canula is too long; therefore I have the point of my canula cut short. For an absolutely safe operation I advise all practitioners, particularly those making their first operation, to proceed as follows:

"We first fill the syringe with a physiologic salt solution, insert the canula into the vein, the cock being open and the tourniquet still loose. After blood has been drawn we inject the salt solution. If the point of the syringe does not rest comfortably in the vein, or if the latter has been in any way injured, the injection of the salt solution will at once cause visible infiltration. If this should happen, we withdraw the canula from the vein and try to insert it into another vein. In all circumstances, the greatest care must be taken to see that no portion of the injection proper finds its way out of the vein and under the skin. Disagreeable infiltrations are produced in this way, which are often very painful and may exist for weeks, although they invariably disappear later on. It is for this reason also that we generally select a vein outside of the bend of the elbow, thereby preventing such infiltrations from obstructing the mobility of the joint. Likewise we also inject an additional amount of the salt solution

into the vein after all of the solution proper has been injected, so as to avoid an irritation in the lower part of the vein. If during the injection of the solution the point of the syringe should slip out of the vein or cause any injury to it, a tumefaction will be observed simultaneously with the injection of the fluid, and the patient will complain of a burning sensation. The needle is withdrawn at once, the tourniquet is adjusted once more, and a reasonable flow of blood is permitted, as we have found this to be the best way of preventing the formation of an infiltration. When the injection has been properly done, as regards technique, the patients have no pain whatever apart from that caused by the introduction of the canula."

For the present, it is impossible to safely decide by which method of administration the best results may be obtained in respect of permanency of the cure.[1]

It is obvious that in administering an intravenous injection, very large quantities of this potent substance will pass through the blood-stream for some time and act vigourously upon the spirochetal foci they may encounter. However, as the remedy is very rapidly eliminated, those foci not reached by the substance will remain unaffected. In the subcutaneous and intramuscular application too, the larger part of the substance is absorbed in the beginning. After two or three days however, an inflammatory wall is formed around the deposit, and a slow uniform absorption continues for a long while.

Even when necrosis occurs, an almost complete absorption may take place. For instance, 0.45 gm. of the neutral emulsion was administered to Mrs. M. subcutaneously on August 28th. As late as the fifth week a necrotization of the infiltration was observed. It was totally removed on

[1] While this paper was in the hands of the printer, Ehrlich having received additional information, announced his belief in the superiority of the intravenous method of injection. Exact proofs, by which a comparison might be possible under control, are not yet to be found in our literature. According to my own conception of the subject, as explained elsewhere in this book, syphilis is rather a disease of the tissues than a disease of the blood; and for this reason, I do not attribute any decisive importance to the method of incorporation of the remedy. Consequently I have been of the opinion that in testing a substance whose toxicity in man has not yet been fully established, the tests should not under all circumstances, be charged with the possible dangers arising from the intravenous method of application. In this way, we encumber the introduction of the new remedy with the possible occurrence of accidents that are not inherent in its very nature. Furthermore, judging from test-tube investigations, I also arrived at the conclusion that hemolysis, or a coarse agglutination of the red blood cells, might possibly be caused by these solutions. A sufficient number of investigations—one thousand, according to Ehrlich—not having shown that the intravenous method is attended by any special danger, we are in duty bound to investigate whether or not the intravenous injection is as devoid of danger as the subcutaneous and intramuscular methods, or whether a more favourable action justifies a correspondingly larger risk of danger.

October 24th, and only 1.9 mgm. of arsenic was found, corresponding to about 6 mgm. of salvarsan.

To be sure, all methods have resulted in excellent effects upon the symptoms. The intravenous injection is painless, but it is frequently accompanied by fever, chills, vomiting and diarrhea. The subcutaneous and intramuscular injection of neutral suspensions are moderately painful, and it must be admitted that they sometimes produce painful infiltrations and even abscesses and necroses.

I was the first to point out, while at Königsberg, that necroses had suddenly begun to occur more frequently. We had treated about eight hundred cases when we saw the first instance of necrosis. A thorough investigation showed that necroses mostly occurred in cases treated by two particular assistants who had been using certain preparations, while in the cases treated by myself and the other assistants, necroses occurred but very rarely. We therefore concluded that very much depends upon an exact method of technique.

It is not always easy to administer the subcutaneous injection exactly under the skin, particularly in the case of stout individuals in whom the subcutaneous fatty layer is very tightly adherent to its substratum. In these cases unless due care is exercised, the point of the needle will generally reach the fatty tissue, or it may find its way into the cutis or even into the fascia; and this will at once produce a large wheal of infiltration. In such a case the injection must be interrupted immediately and care taken to have the point of the needle remain freely movable between the skin and fascia, so that the injected mass will be distributed and scattered by subsequent massage.

Favourable conditions are offered by the skin of the back, whereas the skin of the thorax at the lower ribs is unfavourable. This is shown by the fact that when we had used that spot for some time, in order that patients with inflammatory reaction could rest in greater comfort, necroses and large infiltrations became conspicuously frequent. We also consider it to be particularly important that the injected mass be widely distributed and that the site of injection be very thoroughly massaged, inasmuch as the quantity of the mass deposited at one point is of great importance as regards necrosis.

There can be no doubt that aside from the individual sensitiveness, the technique of the application plays an important part. There is a great difference whether or not the arsenic preparation is injected under the skin in the muscle, or faultily in the skin or in the fascia. This preparation in

any form, whether in acid or alkaline solution and likewise in neutral suspension, always produces a disturbance of the osmotic condition of the neighbouring cells, injuring them and in certain circumstances causing their destruction. If it has been properly injected under the skin or into the muscle, most of it will be absorbed within one or two days and the edematous infiltration caused by the remainder of the preparation will not expose the tissues to sufficient pressure to interfere with circulation. When the liquid is injected into the skin or into the fascia, absorption of the mass is very difficult in the beginning. It may even be entirely prevented and then the injurious action of the arsenic fully asserts itself. The reactive inflammatory infiltration is thereby also greatly increased; and there is a diminution of the blood-supply of the dense and comparatively poorly vascularized tissues (cutis vera, fasciæ), to the extent of readily facilitating the development of necrosis, this being also assisted by the vigourous reducing action of arsenic.

For this reason we insert the needles at two different points and also distribute the mass to be injected still further by moving about the point of the needle while making the injection. This makes it possible for the four or five c.c. of the suspension to be deposited in many places under the cutis. Thus we avoid injection into the dorsal musculature, because it offers a more favourable opportunity for the development of necrosis; for it is clear that the ever-present infiltration, as well as a possible necrosis, the extent of which is always considerable, are of graver importance occurring in the muscle than when they occur in the skin.

Ever since we have insisted upon the most exact technique we have not seen a single case of necrosis. Still we are endeavouring to devise additional improvements in the method of subcutaneous injection, as we do not believe that the subcutaneous introduction of the preparation, particularly in the case of feeble individuals, can possibly be replaced by other methods. It should be remembered that the comparative painlessness and the mild yet positive therapeutic effect of the neutral suspension have greatly facilitated the introduction of the remedy. Therefore every improvement in the subcutaneous method of application must necessarily be gladly received, because in the main it is the most suitable method for general practice.

As compared with the acid and alkaline solutions, particularly those of the earliest period which produced great pain and high fever, though their superior effect has never been demonstrated, the neutral emulsion is a very great improvement.

All methods involving the use of methyl alcohol should be rejected.

Likewise the intragluteal application appears to be objectionable, as I have seen three cases of peroneal paralysis. This cannot be avoided with certainty in any case, inasmuch as we cannot estimate the size and density of the infiltration, the formation of which even the most careful technique cannot prevent.

The most agreeable method of preparation is made by mixing the salvarsan with paraffine or olive-oil. Without definitely rejecting it, it does not seem to me to be sufficiently effective, possibly owing to the size of the grain of the original substance as contrasted with the fine precipitation of the neutral suspension. In view of the slight toxicity of the remedy, it is unnecessary to divide the dose into smaller doses of 0.1 gm. each and in this way administer them to ambulant patients. By this method under certain conditions, painful infiltrations are caused in many places; and owing to the different periods in which they were deposited, they persist unnecessarily long. To arrive at a definite conclusion in this respect, it will be necessary to proceed systematically with investigations on a large scale. But the difficulty in determining the superiority of one particular method as compared with other methods may be judged, according to Professor Lockemann, by the fact that elimination during the first few days, when the maximum absorption takes place, differs greatly in amount even when the same technique is employed.

Elimination of Arsenic Through the Urine.—Fischer and Hoppe have made a careful study of the elimination of salvarsan (*Münchener medizinische Wochenschrift*, 1910, No. 29). After injecting the alkaline solution they found:

1. Elimination of Arsenic Through the Urine

CASE 1.—S., paralytic, received 0.1 gm. (= about 0.04 gm. arsenic) subcutaneously. The elimination through the urine was as follows:

1st	day,	0.0033	gm. arsenic
2d	"	0.0018	" "
3d	"	0.0022	" "
4th	"	0.0026	" "
5th	"	0.0034	" "
6th	"	0.0021	" "
7th	"	0.0018	" "
8th	"	traces	
9th	"	"	
10th	"	negative	

Total amount eliminated through the urine = 0.0172 gm. arsenic.

CASE 2.—W., paralytic, received 0.3 gm. (=about 0.12 gm. arsenic) subcutaneously. Elimination through the urine:

1st	day,	0.0051 gm.	arsenic
2d	"	0.0064 "	"
3d	"	0.0069 "	"
4th	"	0.0061 "	"
5th	"	0.0058 "	"
6th	"	0.0044 "	"
7th	"	0.0068 "	"
8th	"	0.0029 "	"
9th	"	0.0034 "	"
10th	"	0.0028 "	"
11th	"	traces	
12th	"	"	
13th	"	negative	

Total amount eliminated through the urine = 0.0506 gm. arsenic.

Other cases of paralysis, in which the usual dose of 0.3 gm. was administered, were also examined. The result was the same in all. The elimination ceased by the twelfth to the fourteenth day. It was also observed that though the amount of salvarsan injected was the same, i.e., 0.3 gm., the amount of arsenic recovered from the urine varied from 0.02 to 0.07 gm.

The elimination in the case of epileptics with healthy renal function was somewhat different from that in the paralytics. Thus:

CASE.—R., received 0.15 gm. (= 0.06 gm. arsenic) subcutaneously. The urine contained:

1st	day,	0.0058 gm.	arsenic
2d	"	0.0062 "	"
3d	"	0.0051 "	"
4th	"	traces	
5th	"	negative	

In another epileptic, stronger than the preceding, who received 0.3 gm. salvarsan, arsenic was also no longer found in the urine on the fifth day. Thus epileptics having sound kidneys eliminate arsenic far more rapidly than paralytics.

In a similar way arsenic was also eliminated by vigourous syphilitics at the Magdeburg Hospital. The urine of twenty-five patients was investigated, with the result that but a few of the patients, to all of whom 0.3

gm. had been administered subcutaneously, still showed some arsenic in their urine on the fifth day, but on the tenth day the urine of all of them was free of arsenic.

After the intravenous injection, arsenic was eliminated much more rapidly and completely than after the subcutaneous method.

Paralytics given 0.3 gm. intravenously:

1st day, 0.0072 gm. arsenic was found
2d " 0.0792 " " " "
3d " 0.0053 " " " "
4th " negative

Investigations in other patients showed the same result, the excretion of arsenic having been completed within two to three days.

It is well known that arsenophenylglycin is also assimilated in sufficient quantity when administered by rectum. Experiments with the new remedy however, show that when administered by rectum, slight traces only are excreted through the urine.

Thus on the 1st day, 0.0019 gm. arsenic was found
2d " 0.0016 " " " "
3d " negative

Therefore large quantities could not have been absorbed.

II. Elimination of Arsenic Through the Intestine

It is known that atoxyl and arsacetin are rapidly and almost completely eliminated through the urine. The investigations with arsenophenylglycin also show that quite considerable amounts are passed through the intestine. Salvarsan also causes a similar elimination. During the three first days after an intramuscular injection of 0.3 gm., the excrement contained 0.0062 gm. arsenic; from the fourth to the sixth day arsenic was plainly observed and even on the tenth day its presence could still be determined.

In the excrement of the first three days, of the total of 0.0062 gm. arsenic there were found:

In watery extract.....0.0012 gm. arsenic
In extract with HCl....0.0031 " "
In soaps .....-———
In albumin.....———
In lecithin.....0.0019 " "

While arsenic is excreted through the urine in two or three days when injected intravenously, elimination through the intestine takes longer, as arsenic was still found in the feces on the fifth and sixth days.

III. The Retention of Salvarsan in the Body

According to Ehrlich, the new arsenic preparation is not organotropic. Consequently we would not expect to find any considerable amount of arsenic in the organs. In the Magdeburg-Altstadt Hospital a female patient was brought to autopsy fourteen days after an injection, having died of intercurrent disease. In the organs that were examined, arsenic could not be found; but the gluteus muscle, into which the injection had been made, contained a considerable quantity of arsenic. This proves that after an intramuscular injection, a considerable amount of arsenic may be retained without being noticed. Thirty-six days after an injection, another woman was brought to autopsy (sepsis of the nose). Here too, considerable quantities of arsenic (about 0.01 gm.) were found in the gluteus muscle.

Salvarsan seems to disappear from the blood at the same time that it disappears from the urine and feces. In thirty c.c. of blood taken on the fourteenth day after the injection, arsenic could no longer be found. In thirty-nine c.c. of blood taken on the second day succeeding the injection, the presence of arsenic was determined to a certainty by the use of lecithin prepared according to Peritz's method; while in the remainder of the blood the amount of arsenic was considerably diminished.

In thirty cases Fraenkel and Grouven studied the presence of arsenic in the urine quantitatively and found that during the first eight days varying amounts, generally from six to twelve mgm. were found in twenty-four hours' urine; about six to eight mgm. during the second week; and practically none during the third week. In but a very few cases however, two mgm. were found, and in one case nine mgm.

Greven gives the following figures ("Beginn und Dauer der Arsenausscheidung im Urin nach Anwendung des Ehrlich-Hataschen Präparates Dioxydiamidoarsenobenzol," *Münchener medizinische Wochenschrift*, 1910, No. 40, page 2080):

A. Beginning of the Elimination of Arsenic Through the Urine

Salvarsan			First Urine Passed After the Injection[1]	
Dose (Intragluteal)	Time of Injection			
	Date	Time of Day	Time of Day	Result of Examination
0.6 gm.	July 29th	10.30 A.M.	11.00 A.M.	Arsenic present
0.45 "	" "	10.45 "	11.45 "	" "
0.6 "	" 30th	11.00 "	12.00 NOON	" "
0.45 "	August 6th	12.45 P.M.	1.45 P.M.	" "
0.6 "	" "	1.00 "	2.00 "	" "
0.45 "	" 9th	7.10 "	7.35 "	" "

B. Duration of the Elimination of Arsenic Through the Urine

With reference to the method of application we must differentiate between the subcutaneous and the intramuscular methods. In addition, there is another difference to be considered. In one portion of the cases salvarsan alone was administered and in the other portion a course of mercury was also administered, five to ten days later.

1. Cases Treated with Salvarsan Alone

Salvarsan		Elimination of Arsenic Through the Urine
Dose	Method	Duration
0.4 gm.	Subcutaneous (left scapula)	Fourteen days (average of two cases)
0.45 gm.	Intramuscular (in both buttocks)	Seventeen days (average of four cases)
0.6 gm.	Intramuscular (in both buttocks)	Eighteen days (average of two cases)

[1] For the sake of accuracy, the last urine passed before the injection was also examined in every case for arsenic. In this way it was possible to determine whether or not the patient was already taking medicine in which arsenic was present.

2. Cases Treated with Mercury Also

Salvarsan		Elimination of Arsenic Through the Urine
Dose	Method	Duration
0.35 to 0.4 gm.	Subcutaneous (left scapula)	Twenty days (average of four cases)
0.5 gm.	Subcutaneous (left scapula)	Twenty-two days (average of two cases)
0.6 gm.	Intramuscular (in both buttocks)	Twenty-five days (one case)

Professor Lockemann, director of the chemical division of the Royal Institute for Infectious Diseases, very carefully investigated the elimination of arsenic in cases in which an acid solution had been injected and he will publish his findings elsewhere. These painstaking investigations, which Professor Lockemann has permitted me to copy in part, have not yet been fully completed and for this reason the excretion in the later periods only have been principally considered.

The amounts excreted are very small, and during the period of the investigation, the seventh to the twenty-seventh day, they differ but little from each other. In one case (H——g) arsenic could no longer be determined on the thirty-sixth day, while in the parallel case (H——ck), arsenic was still found on the same day. Both cases recovered satisfactorily, but H——ck's case improved the more rapidly of the two.

It seems that after the major portion of the arsenic has been excreted during the first days, the elimination proceeds quite uniformly, while the remaining deposit which is surrounded by an inflammatory wall of infiltration, is gradually being absorbed by the tissues.

Elimination of Arsenic Through the Urine After the Injection of Salvarsan

(The quantities of arsenic are given in mmgm. = 1/1000 mgm. = milliogramm)

FEMALES

H——g. April 19, 1910 11 A.M., 0.3 gm. acid solution, intramuscular	7th Day April 25th **90**	7th Night (missing)	8th Day April 26th **260**	8th Night April 26th, 27th **90**
	9th Day April 27th **20**	9th Night April 27th, 28th **70**	10th Day April 28th **30**	10th Night April 28th, 29th **10**
	11th Day April 29th **15**	11th Night April 29th, 30th **15**	12th Day April 30th **45**	12th Night April 30th, May 1st **2**
	14th Day and Night May 2d, 3d **10**		36th Day and Night May 24th, 25th **Negative**	
H——ck. April 19, 1910 11 A.M., 0.3 gm. acid solution, intramuscular	11th Day April 29th **20**	11th Night April 29th, 30th **25**	21st Day May 9th **15**	24th Day and Night May 12th, 13th **10**	36th Day and Night May 24th, 25th **30**
G——. April 28, 1910 10.30 A.M., 0.3 gm. acid solution, intramuscular	11th Day and Night May 8th, 9th **50**		14th Night May 12th, 13th **60**	27th Day and Night May 24th, 25th **30**	

MALES

D——. April 13, 1910 11 A.M., 0.25 gm. acid solution, intramuscular	7th Day April 19th **110**	7th Night April 19th, 20th **85**	8th Day April 20th **40**	8th Night April 20th, 21st **110**
	9th Day April 21st **70**	9th Night April 21st, 22d **90**	12th Day April 24th **30**	12th Night April 24th, 25th **60**
	15th Day and Night April 27th, 28th **60**		20th Day May 2d **10**	

N——. April 30, 1910 0.3 gm. acid solution, intramuscular	4th Day May 3d **100**	4th Night May 3d, 4th **75**	10th Day and Night May 9th, 10th **50**		
P——. June 1, 1910 11 A.M., 0.5 gm. acid solution, intramuscular	6th Night June 6th, 7th **30**	7th Day June 7th **30**	7th Night June 7th, 8th **50**	8th Day June 8th **40**	14th and 15th Day June 14th, 15th **30**

As to the elimination in the first days after the injection we have the following tabulated data:

MALES

E——. May 3, 1910 0.4 gm. acid solution, intramuscular	1st Day May 3d 10 A.M. to 7 P.M. **4.15**	1st Night May 3d, 4th **1.83**	5th Day May 7th **1.59**	5th Night May 7th, 8th **1.88**
G——. May 3, 1910 0.3 gm. acid solution, intramuscular	1st Day May 3d 10 A.M. to 7 P.M. **0.63**	1st Night May 3d, 4th **1.50**	5th Day May 7th **1.16**	5th Night May 7th, 8th **1.55**

We can see from these figures how absorption and elimination differ in the first few days, although the administration is the same; and we can thus readily understand the differences in the therapeutic effects of the remedy.

REVIEW OF THE LITERATURE

The literature relating to the treatment of syphilis with Salvarsan has grown to such an extent that only the principal works can be referred to:

Ehrlich: "Ueber den jetzigen Stand der Chemotherapie" (Berichte der deutschen chemischen Gesellschaft, XXXII, I.).

Ehrlich: "Ueber moderne Chemotherapie" (Verhandlungen der deutschen dermatologischen Gesellschaft, X. Kongress, Frankfurt a. M.).

Ehrlich: "Chemotherapie von Infektionskrankheiten" (*Zeitschrift für ärztliche Fortbildung*, 1909, 23).

Alt: *Münchener medizinische Wochenschrift*, 15, III, 1910.

Iversen: *Münchener medizinische Wochenschrift*, 17, III, 1910.

Ehrlich: "Allgemeines über Chemotherapie," 27. Kongress für innere Medizin, Wiesbaden, 1910.

Hata: *Ibidem.*

Hoppe and Schreiber: Ueber die Behandlung der Syphilis und der metasyphilitischen Erkrankungen mit dem neuen Ehrlich-Hataschen Arsenpräparat. *Ibidem.*

Wechselmann: "Chemotherapie der Syphilis," Verhandlungen der freien Vereinigung für Mikrobiologie, 20, V, 1910 (*Zentralblatt für Bakteriologie*, 47, Bd., Beiheft Referate).

Discussion

Hoffmann believes that most of the cases thus far shown also get well clinically with mercury and iodine. He insists that all cases in which injury has been caused by the new remedy be published—a policy which has not always been done immediately in regard to Ehrlich's preparation. The superiority of salvarsan over mercury had not yet been demonstrated.

Uhlenhuth refers to his works on the arsenic treatment of spirillosis, particularly with atoxyl in syphilis and with atoxylate of mercury, which

has been found to be effective in animal experiments as well as in human pathology.

Tomaszewski refers to the specific effect of salvarsan, investigated by him in syphilis in rabbits.

Wechselmann, referring to Hoffmann, points out the dangers of the mercury treatment and especially of the insoluble salts, even if correctly administered.

Ehrlich develops the formula of the new remedy and refers to the differences between the remedy and atoxyl. The effect depends upon the arsenic residue (arsenrest), while the lateral groups bring about the primary anchoring to the parasites.

Wechselmann: "Ueber die Behandlung der Syphilis mit Dioxydiamidoarsenobenzol." (Paper read before the Berlin Medical Society, see *Berliner klinische Wochenschrift*, 1910, No. 27.)

During the discussion of Wechselmann's paper before the Berlin Medical Society (June 22, 1910), Leonor Michaelis reported the following in regard to two cases treated by him with salvarsan:

> The first patient had acquired syphilis in 1906; took eight courses of mercury under direction of Dr. Brunck and once also received fifteen atoxyl injections. This is important, as it goes to show that the effect of atoxyl does not even approach that of salvarsan. Furthermore the patient had been repeatedly treated with iodide of potassium. Since 1907, he has had a saddle-nose and also ulcers on both sides of the uvula. On the day of the injection, the uvula seemed about to fall off. For half a year he showed no reaction to mercury and iodine. Injection eight days ago. At the present time only the remains of the ulcers are visible. The healing process commenced on the third day after the injection, with healthy reddening of the margins of the ulcers.
>
> The second patient had an idiosyncrasy towards mercury. While he was being treated with minimal doses of mercury, soon after having been infected with syphilis, he suffered from rigours; his entire skin became intensely red and peeled off in shreds. Of course, the small doses of mercury failed to do him any good. Almost his entire body was covered with a papular syphilide; he also had palmar psoriasis, papules on the back of his hand and small excrescences on the eye. On June 9th, 0.3 gm. of salvarsan was injected, no pain being experienced. On June 22d, the exanthem had disappeared and only a few spots of pigment remained on the back of the hand. According to the patient, the papules began to recede on his forehead and scalp, on the third day after the injection.

Then Alt reported on the cases treated with arsenophenylglycin. In sixteen per cent. the Wassermann reaction disappeared, while in twenty-

seven per cent. it was appreciably changed. Old cases remained under continuous control; and to the present date, after a year and a quarter, the Wassermann reaction which had disappeared has not yet reappeared. He stated also that salvarsan influences the blood formation; that it causes a considerable increase in the white blood corpuscles, it exerts a favourable influence upon the lecithin metabolism, it decreases and even entirely eliminates the Wassermann reaction and obviously exerts a favourable result on the clinical symptoms. After intragluteal injections, elimination of arsenic continued for ten to twelve days; while after intravenous injections it is almost completed within two days, traces only being found on the third day.

He then speaks of a case of severest syphilitic icterus. The man had recently been infected with syphilis, his glands were considerably swollen and he had an extensive icterus from which a strong maculo-papular syphilide projected exquisitely. After a single injection of 0.4 gm. of salvarsan the icterus almost completely disappeared within about nine days, while the other symptoms also receded.

A number of relatively recent cases of tabes were treated with the preparation, and in six cases not only the subjective complaints, but also in one case the objective symptoms were improved and an improvement of the general condition, increase of weight, etc., was noted.

Likewise a number of cases of epilepsy of syphilitic origin were improved considerably. Recently two cases of gravest epilepsy were treated with intravenous injection. Four or five seizures occurred daily and the patients' condition indicated the near approach of death. In one of these cases the attacks ceased almost entirely, the patient being without a seizure for five days.

Schreiber remarks: 420 gm. of mercury had been rubbed into a female patient. While these inunctions were being continued, new eruptions appeared. An injection of salvarsan was given and within a few days the symptoms receded. Complete recovery took place within fourteen days. In other patients with numerous plaques, who had been treated with mercury without any success whatever, the plaques disappeared after an injection of salvarsan in every case.

A second injection was given to four patients in whom recurrence took place after four weeks and no complications occurred. Likewise, two pregnant women were injected and in neither instance did the children show any symptoms of syphilis.

It was also established by Professor Heubner, of Göttingen, that after

an injection of the remedy, the formation of methemoglobin did not take place even when the strongest concentration was employed.

Kromayer reported fifteen cases, some of them showing the gravest forms of syphilis. In all of these cases mercury had but little or no effect whatever. They were then treated with salvarsan.

The pathologic anatomy of some of these cases was more closely investigated. In two cases there were very extensive ulcerations; ulcers the size of a half dollar on the thigh—large ulcers with subcutaneous gummata and exposure of the bones. Experience has shown that it requires weeks and months for epidermization to take place in these cases. It was indeed a surprise to notice that aside from the absorption of the syphilitic infiltrations, the growth of new skin had taken place in a shorter time than one would ever have imagined possible.

Finally, Tomaszewski reported on seventeen cases rapidly cured.

Spatz, Budapest: "Vorläufige Mitteilungen über 'die mit der Therapia sterilisans magna'" (Ehrlich-Hata-Präparat) behandelten syphilitischen Fälle (*Wiener klinische Wochenschrift*, 1910, No. 27).

Spatz observed the favourable curative effect of the remedy on syphilitic symptoms. In twelve days after the injection, the Wassermann reaction became negative in nine cases. He also reports the following by-effects: For twelve to sixteen hours after the injection a rise of temperature to 102.5° F. Polyuria lasting three days, the daily quantity of urine passed exceeding two quarts. In one case the disappearance of a co-existing psoriasis was observed.

Dr. W. Pick related his experiences with salvarsan at a meeting of the Society of Physicians in Vienna, on June 24th (*Wiener klinische Wochenschrift*, No. 26, 30. VI, 1910). He injected thirty cases with satisfactory results. Pick observed that the temperature of the patients treated with the preparation rose to 102° F., but he has not seen any influence on the Wassermann reaction.

Dr. Dörr reported at the same meeting that he had had success with the preparation. He described the momentary results as having been "actually marvellous." They were as follows:

1. Scleroses, injected previous to the appearance of the secondary stage, in which we demonstrated the syphilitic nature of the affection by examining for spirochetes or by the Wassermann reaction. In these cases the symptoms of the primary affection receded rapidly; and one case injected shortly before the appearance of the secondary stage, was free from all symptoms within one month. Likewise with the other scleroses

injected prophylactically, in which however, the time that has elapsed since the treatment was administered has been too short.

2. Cases in which Ehrlich's preparation was administered after the beginning of the secondary stage, or while in the florid stage of recurrence. Here the symptoms of the skin and mucous membrane, i.e., macular, papular, onticular and lenticular syphilides, papules in the mouth, circumscribed and generalized scleradenitis, completely receded within a few days. The patients temporarily cured, are now only being kept for observation. Up to the present as I have already observed, there has been no recurrence within a period of but one to four weeks.

3. Two cases of malignant syphilis, one being in a soldier, formerly a very strong man who had an extended, crust-covered and ulcerating syphilide of the entire scalp, face, trunk and extremities. For months he had been unsuccessfully treated with mercurial preparations, iodine and Zittmann's decoction. He was greatly debilitated, confined to his bed for weeks and unable to rise, suffering from nocturnal sweats and daily recurring intermittent fever of high degree. Like all other patients, one injection of salvarsan was administered to him; and on account of his decrepit condition, the dose given was only 0.3 gm. After two days the fever, the nocturnal sweats and the pains had left him. On the third day the ulcers began to epidermize and to-day the patient is walking about. He has gained nine pounds in weight and he says he feels perfectly well. All of the ulcerations have healed except one, which is still undergoing epithelization. Before treatment, Chief Staff Surgeon Frühauf had given a fatal prognosis. The second case was that of a woman who, according to the history, had acquired extragenital syphilis five years ago. For four years in spite of all kinds of treatment, she has been suffering from several sluggish ulcerations the size of a palm, two c.m. deep, with wall-like, elevated borders. Two weeks ago 0.4 gm. salvarsan was administered to her. The subjective conditions improved at once, the ulcerations filled up in spite of their size and the meagreness of granulation tissue and a new epithelium is growing from the border inwards towards the centre. In this patient too, the treatment with 0.4 gm. salvarsan had not the slightest disagreeable result, although she was very weak and quite emaciated.

4. Late Luetic Nervous Disorders.—Under this heading, three paralytics must be mentioned to whom we had administered insufficient quantities for experimental posologic purposes; and consequently no effect had been expected. However, two of the patients to whom 0.4 gm. had been given, have materially improved, according to Regimental Sur-

geon Mattauschek. One of them who was suffering from attacks of dizziness, unilateral paresthesia and diplopia, is to-day, three weeks after the injection, absolutely free from the symptoms and ailments mentioned. The second one was suffering from unilateral symptoms, dizziness, headache, disturbances of speech and writing and pronounced disturbance of comprehension and memory. To-day after four weeks, the patient feels more free, he is less forgetful and he is no longer suffering from dizziness and headache. Dr. Mattauschek observed a material improvement of comprehension and memory, as well as the disappearance of the disturbances of writing and speech.

"Whether a permanent cure has been attained so that recurrence will not take place, or whether it may be attained with larger doses, we shall be able to report to you next winter.

"I would only call attention to the fact that the types of syphilis refractory to mercury improve with surprising rapidity after treatment with salvarsan, though they had been stationary for years."

Schreiber and Hoppe: "Ueber die Behandlung der Syphilis mit dem neuen Ehrlich-Hataschen Arsenpräparat" (*Münchener medizinische Wochenschrift*, 1910, No. 27).

These authors have injected over 150 cases. After the intramuscular injection they keep the patients abed for three or four days. They have not observed any disagreeable by-effects, although they had administered thirty intravenous injections at the time this work was in process of publication.

In 84.6 per cent. of cases the Wassermann reaction had changed from positive to negative within fifty days.

Dr. Géronne and Dr. Huggenberg reported fifty-five cases to the Wiesbaden Medical Society (*Berliner klinische Wochenschrift*, 1910, No. 28), of which twelve were treated intramuscularly and the remainder intravenously.

Half an hour after the injection the syphilitic efflorescences began to redden markedly, resembling the Herxheimer reaction; but on other parts of the body which were free from exanthemata, urticarial eruptions were observed. All of these phenomena receded completely after twenty-four hours.

In all cases that were observed for a sufficiently long period, the visible symptoms disappeared, usually with striking rapidity. Ten syphilitic chancres the size of a dime were absorbed within ten to fourteen days. In one case a complicating chancroid remained unaffected. The diminu-

tion in size of the lymphatic glands took place very rapidly; that is, within eight to fourteen days. In most of the cases lymphangitis and slight enlargement of the lymphatic glands remained. From the day after the injection spirochetes could no longer be found, either in the primary lesions or in the secondary ulcerations. In two cases where spirochetes were still found six hours after injection in lesser numbers than before, they appeared to be rolled up and with flattened, irregular spirals. Syphilitic roseola and simple macular exanthemata disappeared within two to five days. Exanthemata with papular efflorescences passed off within three weeks at the most, leaving pigment spots. A hemorrhagic exanthem on the leg receded within eighteen days. A severe impetiginous syphilide on the hairy portion of the scalp and on the back disappeared from the former after sixteen days and from the latter within three weeks. Small moist papules (condylomata lata) healed within fourteen days. Some that were large and ulcerated healed within two to three weeks. A palmar and plantar psoriasis disappeared after ten days; and in a second case but little was to be seen after seven days. In five cases of specific angina the patches healed within seven to ten days. A gummatous orchitis the size of a small fist was but very little larger than the healthy testicle sixteen days after the injection; and a coexisting psoriasis vulgaris showed no symptoms of recurrence. In an interstitial glossitis existing about two years, the conditions improved markedly eight days after the injection and the movement of the tongue was greatly facilitated. In ten cases that were observed from four to ten weeks, the Wassermann reaction became negative. In four cases it remained positive, though two of these were observed for fifty-six and seventy days respectively. In twenty-five cases observed less than four weeks it became negative in only six cases. Two recent cases of primary chancre which still reacted negatively before the injection, became positive eight days thereafter; then became negative fourteen days later and remained so. After a period of observation extending through thirteen weeks, recurrence took place in five cases. Among these were three men whom we had treated with intramuscular or intravenous injections for primary chancre. The clinical symptoms disappeared with striking rapidity, the Wassermann reaction became negative soon after the injection and remained so for several weeks. Then after seven to eight weeks a new erosion took the place of the primary lesion, in which spirochetes were again found. In these cases the Wassermann reaction also became positive again. In a patient with specific angina in which the Wassermann reaction did not change to negative after the treatment, a specific angina reappeared

in about five weeks. In a woman having specific angina and treated with salvarsan the Wassermann reaction became negative and remained so for several weeks. It became positive again eight weeks later, without the appearance of clinical symptoms.

On July 13, 1910, Ledermann presented to the Berlin Medical Society a patient who had been treated for syphilis since 1906. He had an unusually large gummatous ulcer superimposed on a syphilitic base. The patient received 0.5 gm. salvarsan. The necrotic crust of the ulcer had fallen off the day after the injection. Two days later epithelization began; and on the thirteenth day half of the ulcer, which was larger than a man's hand, had been covered with new skin. The epithelial margin advanced from one-half to one c.m. every day.

On the same occasion F. Lesser reported the case of a patient with severe syphilis of the lungs who had been treated with salvarsan and was cured.

The patient had been infected eight years ago. When he came for treatment he was very sick, having a temperature of 100° to 102.2° F., and six per cent. of albumin in the urine. His condition began to improve as early as twenty-four hours after the injection of 0.3 gm. salvarsan. On the fifth day he ceased coughing and his urine contained but one-half of one per cent. of albumin. From the tenth day there was distinctly normal breathing all over his lungs. During the discussion Michaelis stated that the new remedy did not cause any irritation of the kidneys, but on the other hand, actually brought about an improvement in the chronic amyloid as well as the acute syphilitic forms of nephritis.

Neisser: "Ueber das neue Ehrlichsche Mittel. Offener Brief an den Herausgeber" (*Deutsche medizinische Wochenschrift*, No. 26. 30, VII, 1910).

After treating several cases Neisser reports that the spirochetes disappear from primary lesions and condylomata within twenty-four to forty-eight hours after the injection; and furthermore, another proof demonstrating the action of the remedy on the spirochetes, Herxheimer's reaction very often appeared around and about the macular and papular efflorescences.

The syphilitic processes proper receded rapidly, especially ulcerations and the malignant forms of syphilis. He called particular attention to the case of a woman with cerebral syphilis, appearing half a year after the infection, associated with optic neuritis, choked disc, diverse paralyses of the ocular musculature and very severe headache. The patient had already been treated with strenuous courses of mercury and potassium iodide with-

out any effect whatever. Even in this case an injection of 0.3 gm. salvarsan, in combination with iodide of potassium however, caused an unusually rapid disappearance of all subjective and objective symptoms. The Wassermann reaction became negative in only ten per cent. of the cases. He also observed recurrences, but attributed these failures to the fact that the doses administered had been too small.

As far as the technique is concerned, he preferred the intravenous method whenever it was possible. Now and then it was followed by quite an acute rise of temperature to 103° F., and occasionally by vomiting. But after a few hours the temperature would fall again and the patient would feel very well. Arsenic had not been found in the vomitus. Neisser explains that the fever after injection is produced by the destruction of spirochetes and the liberation of toxic products, inasmuch as no fever had been observed in the few non-syphilitic cases that have been treated with salvarsan. Because of the considerable quantity of the solution injected severe local pain and infiltrations were caused by the intramuscular injections; but these symptoms also disappeared entirely within six to eight days.

After an injection he regularly observed a very marked hyperleucocytosis (up to 38,000) which gradually disappears. The cases observed by him in which the positive Wassermann reaction became negative had all come under treatment soon after infection; that is, after the appearance of the primary lesion. For this reason he is inclined to ascribe to the remedy a strong prophylactic power. However, in one case in which the injection had been administered in the presence of an undoubted primary affection with a reaction still negative, the latter slowly became positive, probably because the dose administered was too small.

He also tested the efficiency of the remedy in twelve syphilitic monkeys, of which three were cured, two were possibly cured and the others were not cured; also probably because the doses had been too small.

He had not made any prophylactic experiments, but he did observe that in two of the animals which had been inoculated with syphilis and to which eleven days before inoculation 0.025 gm. per kilo of body weight had been administered, the primary lesion appeared somewhat later than but not so fully developed as in animals inoculated simultaneously but not treated with the remedy.

Dr. Treupel: "Erfahrungen und Erwägungen mit dem neuen Ehrlichschen Mittel by syphilitischen und metasyphilitischen Erkrankungen" (*Deutsche medizinische Wochenschrift*, 1910, No. 30).

Treupel insists that before the treatment is given there should be absolute proof that the case is of a syphilitic or metasyphilitic character. He prefers the intramuscular method of injection, as with it the arsenic is eliminated more slowly, being found in the urine twelve or thirteen days after treatment. As a by-effect after the application of the remedy he observed a desquamation of the facial skin, temporary increase of the blood pressure and a rise of temperature to 102° F. three to five days after the injection. With the intravenous injection the elevation of the temperature was less, according to his observation.

Case 1.—In the case of a physician suffering from syphilis and pulmonary tuberculosis, treatment with mercury was unable to remove the last remains of the infection, namely, papules and plaques on the mucous membranes of the mouth. After treatment with salvarsan the symptoms promptly disappeared. There was no unfavourable influence on the pulmonary tuberculosis. The Wassermann reaction was still positive thirty-five days later.

Case 2.—In the case of another physician, affections of the mucous membrane and typical late roseola recurred repeatedly, although he had been treated with six courses of mercury; but when salvarsan was administered the exanthem disappeared. On the eighth day after the injection however, it reappeared, but disappeared once more during the succeeding few days. A papule on the lower lip reacted by becoming very moist; but up to the present it has not yet decreased in size.

Case 3.—This was the case of a gentleman aged thirty-eight, who had been infected in 1904 and was treated at intervals with mercury in 1906 and 1909. He had suffered from an apoplectic seizure, with paralysis of the eyelid and of the ocular muscles, diplopia and weakness in the left leg. Improvement was rapid after 0.3 gm. salvarsan. After the treatment there remained only a slight weakness of the left eyelid and of the left external rectus muscle. General conditions remained stationary during the following weeks.

Case 4.—Incipient paralysis in a man aged forty-two, infected fifteen years ago. Distinct temporary improvement of the psychic phenomena after an intravenous injection of 0.32 gm. salvarsan. The Wassermann reaction was still positive ninety days later.

Case 5.—Hereditary syphilitic affection of the eyes (keratitis and iritis), slowly healing with several slight recurrences after having been

treated with 0.4 gm. salvarsan, intramuscular injection. Wassermann reaction still positive after eighteen days.

Heinrich Loeb, Mannheim. "Erfahrungen mit Ehrlich's Dioxydiamidoarsenobenzol 606" (*Münchener medizinische Wochenschrift*, 1910, No. 30).

This remedy was administered in thirty-five cases and was highly successful in syphilitics. In a case in which an intravenous injection of 0.14 gm. salvarsan had been administered recurrence was observed. The patient then received four injections of salicylate of mercury. This was followed by a slight albuminuria with many casts. The conditions were somewhat complicated in this case, as the patient had suffered from yellow fever in 1906; and since that time she had complained constantly of headaches. Loeb observed a favourable effect of the remedy's application in a case of verruca plana in a child and lichen chronicus Vidal. Both of these affections were found in conjunction with syphilis.

Glück: "Kurzer Bericht über 109 mit 606 behandelte Luesfälle" (*Münchener medizinische Wochenschrift*, 1910, No. 31).

Glück attempted to diminish the painfulness of the intramuscular application by injecting under the abdominal skin; but that method was not successful as infiltrations were formed. In five cases Glück observed that sixteen to twenty-four hours after injecting the remedy an extensive eruption of wheals appeared all over the body. In two cases an erythema resembling scarlet fever appeared after the injection and disappeared twenty-four hours later, being replaced by a typical macular exanthem. In a woman seven months pregnant the fetus died on the day after the injection. Otherwise there were no untoward secondary phenomena. The remedy always acted favourably upon syphilitic manifestations. Of twenty cases fifteen retained a positive Wassermann reaction twenty-one days after the salvarsan had been administered, while in five cases it became negative on the thirty-fifth to the fortieth day after the injection.

E. Schreiber and J. Hoppe: "Die intravenöse Einspritzung des neuen Ehrlich-Hata Präparats gegen Syphilis" (*Berliner klinische Wochenschrift*, 1910, No. 31).

These authors have given 120 intravenous injections. The effect was generally very rapid. In one patient the positive Wassermann reaction was changed within forty hours.

Neisser and Kutznitzky: "Ueber die Bedeutung des Ehrlichschen Arsenobenzols für die Syphilisbehandlung" (*Berliner klinische Wochenschrift*, 1910, No. 32).

They have thus far treated:

Nine patients with primary syphilis.
Forty-eight patients with secondary syphilis.
Nine patients with tertiary syphilis.
Ten patients with latent syphilis (mostly some years after the infection).
Six patients with cerebral and spinal syphilis.
Six tabetics.
Two paralytics.
Three patients with parenchymatous keratitis.
Three patients without syphilis, i.e., two with psoriasis, one with leukemia.

Apart from the unquestionably successful cases exceptional instances were recorded where a late effect or apparently no effect whatever was observed. Occasionally spirochetes were still found on the ninth and tenth days. Tertiary processes did not show any healing tendency for days and epithelization took place very slowly. In cases of parenchymatous keratitis particularly, a visible effect upon the morbid process could not be observed.

These observations may be explained by the doses administered having been too small, as well as by unfavourable local circulatory conditions. As a result of the latter, a rapid local effect of the remedy circulating in the general lymph-stream is made impossible. It is well known that in the case of tuberculin for instance, the reaction is very slight or absent altogether in typically tuberculous processes which are surrounded by a hard, fibrous induration. The poor result in the case of parenchymatous keratitis becomes plausible when we consider the peculiar position of the cornea in the body as an organ, *sui generis* ("Sonderorgan").

In forty-four per cent. of the cases the positive serum reaction became negative with the Wassermann method, but in only 19.2 per cent. with Stern's modification.

The change never occurred before the thirteenth day after the injection and in most cases from the twentieth to the thirtieth day. However these were all cases in which only 0.3 to 0.4 gm. of salvarsan had been administered, larger doses having been given only more recently.

Intramuscular injections of 0.025 gm. or intravenous injections of 0.015 gm. salvarsan per kilo of body weight were administered to twelve syphilitic monkeys after the primary lesion had disappeared. In three of the animals which were reinoculated with human virus one month after

the injection, typical primary lesions appeared after the usual period of incubation. In three others treated in the same way suspicious-looking infiltrations appeared at the point of inoculation, which healed after a short while. In two of these animals the presence of syphilis can be assumed the more readily, inasmuch as the control animals were unmistakably positive, while in the third animal the control remained negative. Thus in addition to the first three monkeys two additional animals may be considered to have been probably cured, while in the case of the last the cure is doubtful.

Syphilitic neuritis and choked disc are affected favourably, but it is still a question whether or not atrophy of the optic nerve may also be treated with salvarsan.

Pick: "Bericht über die bisherigen Resultate der Behandlung der Syphilis mit dem Präparate von Ehrlich-Hata" (*Wiener klinische Wochenschrift*, 1910, No. 33).

Ten cases of primary sclerosis before the appearance of the eruption and ten cases of sclerosis with secondary phenomena were treated. In six cases of the first group secondary phenomena failed to appear within four to twelve weeks. The scleroses responded promptly by softening, with subsequent diminution in size and rapid epithelization; but a slight induration still remained for a long time and consequently local treatment appeared to be necessary. Sixty-four cases of secondary syphilis were treated. In these cases macular exanthemata disappeared on the third or fourth day and moist papules were covered with epithelium in the same period. Papular eruptions disappeared within six to ten days. The effect on the lymphatic adenitis accompanying the secondary stage was relatively less. Most striking however, was the effect on the lesions of the mucous membranes, which in some cases were no longer visible on the day after the injection and not in a single case after the fourth day. This result was especially noticeable in severe ulcerative cases which had resisted treatment with iodine and mercury for years. Chronic indurative syphilitic glossitis was completely cured in a very short time. The effect in malignant and tertiary syphilis was extraordinarily satisfactory, especially in cases in which the tuberculo-serpiginous syphilides resisted treatment most obstinately. Only one case of hereditary syphilis was treated and in this instance the injection produced a prompt and effective result. In cases of tabes and progressive paralysis distinct cures were not attained, but in a case of cerebral syphilis the result was very favourable. Recurrence took place in two cases. The Wassermann reaction became negative in most cases within

four weeks; but in cases that had received prophylactic treatment and in which the reaction was negative it remained so. The injection was administered intramuscularly under the scapula, after preliminary sterilization of the skin. The by-effects observed were as follows: Fever in one case reaching 103.5° F., frequently also a diminution in the amount of urine passed, loss of appetite, dryness of the throat and acceleration of the pulse. In these cases pyramidon proved to be effective against these reactive phenomena. Malignant syphilis, obstinate lesions of the mucous membranes and prophylactic treatment may be considered the principal indications for the use of the remedy. On July 30, 1910, before the Lower Alsatian Medical Society at Strassburg, Alsace (*Münchener medizinische Wochenschrift*, 16, VIII, 1910, No. 33, page 1765), Wolff reported the results in nine cases, some of them with very pronounced success. Schultz reported seven successful cases and M. Meyer sixteen cases. Among the last mentioned were twelve undoubted cases of paralysis. In four of these the Wassermann reaction was not influenced in the least, probably because the dose had been too small. In four cases the intensity of the reaction temporarily diminished and in the remaining four cases (intravenous injection) the Wassermann reaction disappeared immediately. In none of the cases was a permanent improvement of the paralysis attained and in but one case a temporary remission took place. In a case of acute insanity associated with a recent syphilitic exanthem and swelling of the glands, the latter symptoms receded promptly. In a case of cerebral syphilis with meningitic symptoms and epileptiform attacks, there was some improvement.

Julius Iversen: "Ueber die Behandlung der Syphilis mit dem Präparat 606 Ehrlichs" (*Münchener medizinische Wochenschrift*, 1910, No. 33).

Sixty syphilitics were injected with distinct success. Generally 0.4 or 0.5 gm. salvarsan was injected intravenously and forty-eight hours later an additional dose of 0.3 or 0.4 gm. was administered intramuscularly. The rapidity with which the symptoms disappear after one injection depends upon the extent of the anatomic changes that have taken place. Superficial erosions, roseola, macular syphilides, plaques, specific pharyngitis and angina thus disappear within a few days, while papular and pustular syphilides require ten to fourteen days or longer. Primary scleroses and glandular adenitis are influenced rapidly, although it takes from three to four weeks for them to disappear entirely. Gummata and symptoms of hereditary syphilis are also favourably affected. Examinations of the secretion of primary scleroses and enlarged lymphatic glands showed that the spiro-

chetes disappeared rapidly after the injection. In two cases disappearance of the Wassermann reaction was observed in eight and ten days respectively, as a rule after twenty to forty days. The conclusion may be drawn from these observations that the preparation exerts a specific effect on the spirochetes pallida, as a result of which it is capable of causing the removal of the manifest symptoms of syphilitic infection with the utmost celerity.

Vilmos Viola, Csäktoruga (*Wiener klinische Wochenschrift*, 1910, No. 33).

Dr. Viola briefly suggests that for theoretical and practical purposes the prevalence of syphilis in the Tyrol and Styria should be investigated because of the many arsenic eaters that live there.

Erich Hoffmann, of Bonn: "Die Behandlung der Syphilis mit dem neuen Ehrlich-Hataschen Präparat" (*Medizinische Klinik*, 1910, No. 33).

Hoffmann gives a detailed description of four cases treated with salvarsan, three of which were successful. In the fourth case he observed high fever, acceleration of pulse to 140 per minute, irregular heart-sounds and diminished resonance in the right lower lobe with subsequent serous exudation. These he considered the expression of a central embolic pneumonia with consecutive pleurisy, "probably proceeding from a thrombus in the gluteal muscles, caused by the injection of the strongly acid solution." In one instance after injecting the preparation, Hoffmann observed a slight albuminuria. In two cases after the injection of an acid solution he observed an extension of the cardiac dulness to the right, systolic murmur at the apex and base, exaggerated second pulmonary sound and an increase of the pulse rate from 120 to 160. The author also mentions a fatal case after injection of 0.3 gm. in acid solution, but he does not give any details, as this case is to be published later on.

Alt: "Die neueste Behandlung der Syphilis und ihre Bedeutung für die öffentliche Gesundheitspflege" (*Zeitschrift für Medizinalbeamte*, 1910, No. 14).

Alt again emphasizes the importance to the public welfare of the treatment of syphilis with salvarsan in conjunction with the demonstration of the existence of the disease through the Wassermann reaction.

Kromayer: "Theoretische und praktische Erwägungen über Ehrlich-Hata 606" (*Berliner klinische Wochenschrift*, 1910, No. 34).

Kromayer treated twenty-seven selected cases with the preparation. In three of these cases which were not completely cured after the use of 0.3 gm. of the remedy, success was attained by subsequent treatment with

mercury. Recurrence was observed in five of Kromayer's cases and in four out of sixteen cases the Wassermann reaction changed to negative.

Dr. Maximilian von Zeissl: "Meine bisherigen Erfahrungen mit Ehrlich 606" (*Wiener klinische Wochenschrift*, 1910, No. 32).

Zeissl injected thirty-one cases and he observed rapid improvement in cases with papules of the mucous membrane, gummata on the skin and in iritides. On the third day after the injection a slight rise of temperature was noted. Immediately after the injection the author observed wheals near the site of injection similar to those caused by injections of dionin, but they disappeared within a few minutes. Zeissl advises that the greatest possible caution be taken in administering the preparation to Poles and Italians, who are said to respond with more severe fever reactions. He also prescribes the following diet for the patients after injection: Milk diet, alcohol to be given to potators only; vinegar, citric acid, compote and tobacco prohibited. Zeissl also considers it advisable that injections be administered to the wives of syphilitic men, even though they give a negative Wassermann reaction.

Spatz: "Zweite Mittheilung über die mit der 'Therapie sterilisans magna,' Ehrlich-Hata-Präparat behandelten syphilitischen Fälle" (*Wiener klinische Wochenschrift*, 1910, No. 32).

Through the observation of his cases that reacted to the preparation, Spatz concludes that in view of the virulence of the spirochetes in primary scleroses, it would be advisable to inject 0.5 or 0.6 gm. of salvarsan, while 0.4 gm. would be sufficient for gummatous processes.

Herxheimer: "Arsenobenzol und Syphilis" (*Deutsche medizinische Wochenschrift*, No. 33. 18, VIII, 1910).

Herxheimer administered the preparation in seventy-two cases and he found it to be devoid of danger, as a general rule. He injected as much as 0.5 gm. in neutral suspension subcutaneously. He observed Herxheimer's reaction several times after having injected the remedy. Ulcerating syphilitic processes were influenced most agreeably. Herxheimer also observed a rapid disappearance of the spirochetes and a disappearance of the Wassermann reaction. In comparing the therapeutic treatment with calomel, Herxheimer observed a more rapid effect of salvarsan on the syphilitic symptoms, referring particularly to the mucous membranes and the skin. Two of the cases treated by this author remained uninfluenced by the preparation. One was a primary lesion with double inguinal lymphadenitis and macular eruption on the trunk and one case presented numerous organized papules. Herxheimer believes with others that this

refractory conduct is to be attributed to the probable presence of strains of salvarsan-fast spirochetes. A case of psoriasis was not affected by 0.5 gm. of the preparation, while a case of lichen ruber planus healed a few days after an injection of the same quantity.

H. Isaac: "Ergebnisse mit dem Ehrlichschen Präparat 606" (*Berliner klinische Wochenschrift*, No. 33, August 15, 1910).

In twenty-seven cases the well-known observations were confirmed. Fever rose to 103° F. after intravenous application. The Wassermann reaction remained positive except in one case.

Professor M. von Zeissl: "Ueber weitere 21 mit Ehrlichs 606 behandelte Syphiliskranke" (*Wiener klinische Wochenschrift*, 1910, No. 34).

This author renders a supplementary report on the cases successfully treated with salvarsan. To prevent the development of phlegmon, he recommends that the patient be kept abed for seven days after the injection.

Dr. Braendle and Dr. Clingestein: "Bisherige Erfahrungen mit Ehrlich 606" (*Medizinische Klinik*, 1910, No. 34).

The remedy was administered in twenty-seven cases, at first according to the old Ehrlich method. With this method of treatment these writers observed elevations of temperature up to 103° F. lasting three days. Subsequently, when the preparation was injected according to Wechselmann and Lange's technique, the temperature remained normal and there was hardly any pain. Apart from a favourable influence which is seen in cases of malignant syphilis, affections of the mucous membranes and roseolæ, they observed that papules and small and large papular exanthemata receded quite slowly. The secondary effects observed two or three days after the injection were an increase of the blood pressure, frequent scintillating scotomata, and transitory blindness in one eye, lasting about ten minutes and a small, rapid pulse. In one-quarter of the cases increase of the tendon reflexes and in three cases symptoms of collapse. In but one of the twenty-seven cases the Wassermann reaction became negative.

C. Fraenkel and C. Grouven: "Erfahrungen mit dem Ehrlichschen Mittel 606" (*Münchener medizinische Wochenschrift*, 1910, No. 34).

These authors injected one hundred cases, three of which by the intravenous method; but when one of the latter resulted in death three and a half hours after the injection, the intramuscular method was resumed. In patients at the psychiatric clinic, disappearance of the Wassermann reaction was repeatedly observed after large doses had been administered. No effect was observed on the disturbances which owed their existence to serious lesions of the brain. In the cases of syphilis thus treated they

observed a decided and unusually prompt and favourable influence on the various syphilitic manifestations; and at times these effects were so startling as to surpass the most striking results of mercurial treatment. Primary lesions and secondary exanthemata of the skin and mucous membranes frequently receded within a few days. Moist condylomata were epidermized very rapidly. Inflammations of the periosteum and swelling of the glands showed the most rapid disappearance. Likewise tertiary changes of the skin, mucous membranes and bones were affected most favourably. In a patient with malignant syphilis the effect was especially striking, a similar result being also attained in hereditary syphilis. In a number of cases success was slow or incomplete and a temporary improvement was sometimes followed by a recurrence. Neither could it be stated that the Wassermann reaction had been regularly influenced. Psoriasis, pemphigus and lichen ruber were improved with remarkably satisfactory result. As the result of the observations made by these authors, we may assume that the new preparation is of considerable value and of peculiar importance as a remedy for syphilis.

Professor S. Ehrmann: "Einige Bemerkungen über die Wirkung des neuen Ehrlichschen Präparates 606" (*Wiener klinische Wochenschrift*, 1910, No. 38).

This writer has observed that the remedy generally brings about a satisfactory result.

Dr. Bodo Spiethoff: "Arsenobenzol bei Syphilis. Aus der Hautabtheilung in Jena" (*Münchener medizinische Wochenschrift*, 1910, No. 35).

Spiethoff's experiences relate to fifty cases which resulted favourably in every way. Glandular swellings were least affected in primary lesions. In two cases of secondary syphilis Spiethoff saw the glands recede with remarkable rapidity. In most cases the Wassermann reaction became negative. Among the secondary phenomena in Spiethoff's cases, an epileptic attack brought on by the injection should be mentioned. The patient was a robust man aged thirty-one, with latent, secondary syphilis. He had been transferred to the division for skin diseases from the psychiatric division with the diagnosis of "stupor and latent syphilis." Wassermann reaction positive. He was given 0.3 gm. salvarsan in a monacid solution. Four hours later a convulsion set in, with loss of pupil reflex and increased patellar reflexes. On the termination of the convulsion eneuresis occurred. On recovering consciousness the patient was unaware of the attack and was unable to say that he ever had a similar seizure. His parents declared that their son had never suffered from epilepsy, but it was admitted that he

had a temporary psychic disturbance when he was fourteen years of age. For the past two years he had been remarkably quiet and shy. In this case the preparation had been dissolved in methyl alcohol. Whenever this form of solution was used, Spiethoff occasionally observed scintillating scotomata and in a patient with tabes he once observed the loss of vision in one eye lasting ten minutes. In an anemic woman aged twenty-eight and having syphilis of the throat, death occurred during the night following the injection. She had been given 0.5 gm. salvarsan in a monacid solution. The post-mortem examination showed the following: Tertiary syphilis of the throat, with a high-grade scar-tissue stricture of the pharynx. Cicatrized gummata in the liver. Hypoplasia of the heart and aorta. Phenomena indicative of arsenic intoxication were not observed at the post-mortem examination.

Herxheimer and Schonnefeld: "Weitere Mittheilungen über die Wirkung des Ehrlichschen Arsenobenzols bei Syphilis" (*Medizinische Klinik*, No. 36. 4, IX, 1910).

Up to the middle of August 130 cases were injected, first according to Ehrlich's directions and subsequently according to the method of Wechselmann and Lange. By-effects were not observed. Herxheimer reports that they did not use either the intravenous method advised by Ehrlich nor the intravenous-intramuscular injection as recommended by Iversen. Lesions of the heart, fetid bronchitis and non-syphilitic disturbances of the optic nerve are considered by the authors as contraindications. Doses of 0.2 to 0.5 gm. were generally given and 0.6 gm. was given but once. Local treatment was not administered. Micropapular exanthemata and leucodermata were apparently the least affected by the preparation, while the best results as stated by Herxheimer in his first report, were observed in cases of malignant syphilis and tertiary manifestations. For instance, a syphilitic periostitis of the head the size of a child's fist, disappeared completely six days after the injection. Another patient with an ulcero-serpiginous syphilide of the back and top of the head, who had been treated for fifteen years with repeated recurrences, was discharged cured within twenty-four days after 0.45 gm. salvarsan had been administered. In conclusion the report states that up to the present time the number of cases of syphilis treated had increased to two hundred; and that recurrence was observed in one case thirty-seven days after the injection.

Karl Schwabe: "Ueber die Wirkung des Ehrlichschen Arsenobenzols auf Psoriasis und Lichen ruber planus" (*Münchener medizinische Wochenschrift*, No. 36. 6, IV, 1910).

The well-established favourable action of arsenic in psoriasis induced this author to administer salvarsan in three inveterate cases of psoriasis. In all of them a vigourous reaction of the skin in the form of reddening, desquamation and pruritus occurred two days after the injection of 0.4 or 0.5 gm. salvarsan. Then the infiltrations decreased for several days. In two cases the reparative process ceased, while in the third case the condition actually became worse. Of three cases of lichen ruber planus which had been treated with salvarsan, two remained unaffected by the preparation while the third seemed to have been cured after some days. In this case the result was so good that Professor Herxheimer was led to report this case in his first publication as having been cured, but there was a recurrence at the expiration of ten days. In a case of chronic circumscribed neurodermatitis of six years' standing in a syphilitic patient, a surprising improvement took place twenty-four hours after 0.5 gm. salvarsan had been administered and the violent itching which had previously existed disappeared entirely.

Dr. M. Mondschein (*Wiener klinische Wochenschrift*, 1910, No. 36).

Mondschein reports twenty-five cases in which the injections of salvarsan were successful. Among them was a case of amyloid degeneration of the kidneys and one case of tabes with diastolic murmur at the apex of the heart and an accentuated second pulmonary sound. Both of these cases stood the injection very well.

Dr. Fritz Juliusberg, Posen (*Medizinische Klinik*, 1910, No. 36).

Juliusberg administered doses up to 0.6 gm. The syphilitic phenomena healed more rapidly than under treatment with mercury.

Leonor Michaelis: "110 Fälle von Syphilisbehandlung mit Ehrlich-Hatascher Injektion" (*Berliner klinische Wochenschrift*, 1910, No. 37).

Michaelis treated four patients with choked disc. In three of these the process is receding, while the fourth case has been under observation only for a short while. Leukemia and lymphosarcoma were not affected by salvarsan. The fatal cases resulted from intercurrent diseases. Marasmus is particularly mentioned by Michaelis as a contraindication to the injection of salvarsan.

Schwartz and Flemming: "Ueber das Verhalten des Ehrlich-Hataschen Präparates, des Arsenophenylglycins, des Jodkali und des Sublimat zur Wassermannschen Reaktion" (*Münchener medizinische Wochenschrift*, 1910, No. 37).

These authors demonstrated that the substances above mentioned do not possess hemolytic properties in any proportion of dilution. In-

hibition of hemolysis occurred only in the presence of very high concentration.

Dr. Karl Junkermann: "Behandlung der Syphilis mit Ehrlich-Hata 606" (*Medizinische Klinik*, 1910, No. 35).

Twenty-five cases which have been treated with the remedy are reported. In all cases but one—a nursing infant—the result was successful. This child arrived at the clinic in a moribund condition and was given 0.02 gm. of the remedy. Death occurred soon thereafter. The post-mortem examination failed to show any indications of syphilis. Neither was it possible to determine that injury had been caused by the injection.

Dr. Moritz Ivanyi: "Meine Erfahrungen mit '606' " (*Wiener klinische Wochenschrift*, 1910, No. 36).

Ivanyi observed that in the case of a paralytic, a dose of 0.5 gm. at first resulted in an improvement. This was followed by a general deterioration. The case of a syphilitic aged forty-six suffering from diabetes is interesting, as no sugar was found in his urine six days after the injection. During a long period of observation the urine remained normal.

Von Grosz: "Arsenobenzol gegen syphilitische Augenleiden" (*Deutsche medizinische Wochenschrift*, 1910, No. 37).

He considers atrophy of the optic nerve a contraindication. A case of primary lesion of the conjunctiva, three cases of syphilitic iritis, one case of syphilitic keratitis, one case of syphilitic scleritis, two cases of syphilitic chorioretinitis, six cases of parenchymatous keratitis with congenital syphilis were all treated successfully.

Gennerich, Kiel: "Ueber Syphilis behandlung mit Ehrlich-Hata 606" (*Berliner klinische Wochenschrift*, 1910, No. 38).

Gennerich from his own experience also states that the general effect of the remedy is a favourable one.

The Jarisch-Herxheimer reaction occurs with striking frequency almost regularly. Cases of optic neuritis were injected without any injurious effect. The serum reaction gave the following results:

1. In recent cases of syphilis Ehrlich's treatment causes the serum reaction to run parallel with the clinical course of the disease; and this as a rule more promptly than in cases in which mercurial treatment is employed.

2. The negative serum reaction is only of relative importance in all stages of syphilis, as the reaction is no longer capable of indicating a local syphilis.

3. At present the result of the Ehrlich treatment is most favourable, clinically as well as serologically, when a sufficiently large dose has been administered. It also seems that preliminary treatment with mercury is an advantage except in malignant cases.

The following cases are worth mentioning:

CASE 1.—G., chief gunner's mate. Infected July 1905, at Singapore. Course of treatment from March to April 1905, consisting of 80 gm. grey ointment. June 17, 1910, coryza and difficulty in swallowing. On June 20th, was received at the hospital with ulcerous necrosis of both tonsils and posterior nasopharynx. Complete sequestration of the right lower turbinate. July 30th, discharged; able to report for duty after six injections of calomel and one of grey oil. Patient's weight had increased nearly seven pounds. On the afternoon of the same day a violent attack of excitement lasting two hours set in, followed by violent headache, dizziness and fainting. On July 31st, was readmitted to Marine Hospital at Kiel. *Status:* Sensorium benumbed; right nostril completely clogged; an ulcer the size of a quarter, in the pharynx; the cranial vault exceedingly sensitive; marked paralysis of limbs. In spite of inunctions of grey oil administered for eleven days, the condition grew gradually worse. On August 14th, only Zittmann's decoction could be given because of intestinal hemorrhage. August 17th, the hemorrhage having ceased, he was removed to the Kiel-Wik Hospital. *Status:* Sensorium benumbed; general paralysis of face, particularly on the right side and tongue, the latter protruding to the teeth and deviating to the right; also paralysis of all the limbs; swallowing very difficult; speech, bulbar and indistinct; unable to stand; when supported on both sides the patient is able to move his legs a little forward; he still can lift his arms a little; owing to stiffness of the fingers he is unable to grasp a tumbler; complete superficial and deep anesthesia; exaggerated reflexes; diplopia observed previously; movement of the head causes tonic and clonic spasms of the entire body; flow of sanies from the right nostril. At 8 P.M., August 18th, an injection of 0.6 gm. salvarsan was administered. August 19th, the patient was hardly recognizable. He is perfectly conscious, gives clear and comprehensible answers; decided amnesia for all occurrences during the last two months, only remembering most violent headaches in left temple; site of injection continually insensitive; the tongue protruding beyond the teeth, still deviates to the right; lips tightly sealed; diplopia absent; fairly vigourous handshake; rises and walks about without assistance; nose entirely clear and dry; lower right turbinate gone; deep sensation returned; reflexes increased; tinnitus in both ears (as before the injection). August 21st, tinnitus gone. August 22d, sensation at the site of injection beginning to return. August 23d, the tongue can be held in the median line. August 24th, sensation completely restored; reflexes still increased; no Romberg; patient able to read. August 27th, nothing abnormal; intellect not impaired; gain in weight nearly seven pounds.

SERUM REACTION:

August 18th −	August 22d to 30th −
August 19th + (weakly)	September 1st −
August 20th −	September 2d −
August 21st −	September 3d −

In this case the curative effect was actually marvellous. From the pathologic and anatomic points of view the case gave the clinical picture of paresis. It was most probably one of vascular disease (mesarteritis), which in consequence of increasing interference with the circulation had produced severe anemia, but had not yet brought about destructive processes in the brain substance. In spite of its somewhat sudden appearance it is not likely that the attack of July 30th was of an apoplectic nature. This view is also in harmony with the fact that the patient does not clearly remember anything after June 20th, although at present he is fully conscious of events preceding that date and his intelligence has been restored to normal.

CASE 2.—M., sailor, infection and chancre in July 1909; roseola in August 1909. First course of treatment September to October 1909, consisting of ten injections of calomel. In April, recurrence of exanthem. Second course of treatment from April to May 1910; five injections of calomel and five of grey oil. Third course of treatment intermittent and without any clinical symptoms; it began August 8, 1910 with two injections of calomel. On the evening of August 14th, while in bed he became aware of a paralysis of the right arm and leg. August 17th, bulbar symptoms appeared; difficulty in swallowing; sensory aphasia. August 18th, violent tremour and deviation of tongue to the right; moderate atrophy of the muscles of the right arm and leg. August 22d, right pupil reacts more slowly than the left; Babinski +. August 23d, spinal puncture; spinal fluid gives distinct opalescence after the addition of magnesium sulphate; increased lymphocytosis. From August 17th to 24th, inunctions of mercury and iodide of potassium; mercury then discontinued because of albumin in the urine; increasing symptoms of paralysis. August 25th, *status præsens:* Moderately vigourous man of medium stature, with pale and expressionless features; right arm completely paralyzed, musculature markedly atrophied; right leg can be moved voluntarily only one-quarter of its normal capacity; muscles very feeble; cannot rise nor stand upright unassisted; neither can he close his lips nor whistle; no difficulty in swallowing; the tongue can be readily protruded beyond the teeth, but deviates to the right; right pupil reacts more slowly than the left; background of the left eye normal; right papilla very indistinct, not sharply defined; sensorial aphasia; patient is no longer able to tell the various officers' ranks, nor the factory

in which his father is employed; considerable disturbance of intellect; seems about as well informed as a schoolboy ten or twelve years old; slight anesthesia; on the right side the patellar reflex is increased, epigastric and cremasteric reflexes are suspended, and the tendo Achilles reflex is absent; Babinski, right side, +. At 6 P.M., 0.6 gm. salvarsan was administered. No pain followed the injection.

On the following morning (August 26th) patient feels quite well and looks much better; right arm freely movable at the elbow to a right angle; right leg again freely movable; sensorial aphasia and intelligence have distinctly improved. August 28th, slight movement of the fingers. August 30th, elbow joint has almost the normal range of motion; for the first time the wrist and shoulder joints can move voluntarily; motion of fingers is considerably improved. September 1st, tongue still deviates a little to the right; mobility of right shoulder, elbow and wrist joints increasing rapidly; considerable increase of bodily strength; this morning the hand is fully extended for the first time; right leg moves easily; patient stands and walks without difficulty; right patellar reflex increased; right epigastric and cremasteric reflexes still suspended. Babinski, right side, slightly +. September 2d, the improvement continues; right arm can be raised above the horizontal; fingers can be bent and extended fully; moderately vigourous handshake; right papilla (resembling choked disc) still somewhat indistinct; normal vision on both sides.

SERUM REACTION:

August 26th −	August 30th −
August 27th + (faintly)	September 2d −
August 29th −	September 3d −

The early appearance of a hemiparaplegia is rather surprising in a man who has received good treatment. This being due to an apoplectic seizure in this case, it is natural that such an immediate cure by salvarsan as occurred in the case of G. was not to have been expected. However, the early and continuous improvement was astonishing. There was in all probability an extravasation into the inner capsule without injury to the cerebral cells. The optic neuritis on the right side was not affected detrimentally by the treatment. The parallel case referred to above (fireman P., H.M.S. *Bremen*, San. Ber., 1908–9) greatly resembled the present case, not only as regards the early appearance of the apoplexy but also as to the symptoms of paralysis. Treatment with mercury for months resulted in very slight improvement.

He was subsequently retired because of disability, with the right leg markedly paretic and the right arm totally paralyzed. In the present instance the positive change of the serum reaction is also remarkable.

CASE 3.—H., chief engineer's mate on torpedo boat. Referred on August 17, 1910, with fresh gonorrhea and apparent gonorrheal arthritis in the right hip. Moist papules on the penis, containing fairly large number of spirochetes pallida. Infected with syphilis in July 1906; chancre present. Eight weeks later ulcer in mouth. Received inunctions in August and September 1906; likewise in February and March 1907. In February 1908, twelve injections of grey oil. Present infection with gonorrhea on July 15, 1910. Since August 10th, violent pains in the right hip. Cannot move his right leg since August 14th. Marked atrophy of muscles of the right leg; very poor appetite. At 7.30 P.M., on August 18th, 0.65 gm. salvarsan was administered. Slight pain at the site of injection lasting barely two hours; one hour after injection the pain in the right hip had decreased sufficiently to again permit of movement of the leg; about midnight the leg was freely movable; three hours later there was no pain whatever. August 19th, right hip-joint is without pain and freely movable; general condition very good, no complaint; papules on penis dry; patient can stand without pain; considerable weakness in the right leg. August 22d, syphilitic symptoms no longer visible; during the evening swelling and pain appeared in the right ankle-joint. August 25th, daily subcutaneous injections of collargol have been administered, with the result that the right ankle-joint is painless and can be moved; swelling somewhat decreased; treatment with collargol and the usual methods continued. August 30th, hip-joint normal; ankle-joint moves freely; no swelling; patient rises without any difficulty.

SERUM REACTION:

August 18th −	August 22d −
August 19th −	August 27th −
August 20th + (slightly)	August 30th −
August 21st −	September 3d −

In this case it is seen that the localized syphilitic rheumatism in the joints was cured by salvarsan with surprising rapidity. The evanescence of the positive serum reaction in this case is also very remarkable.

Dr. M. Gourwitsch and Dr. S. Bormann: "Das Ehrlich-Hatasche Präparat 606" (*Deutsche medizinische Wochenschrift*, 1910, No. 38).

Among the observations of these authors the following by-effects should be prominently mentioned: 1. In a female patient who before salvarsan was injected into the back, had been injected in the gluteal region with salicylate of mercury, without showing any reaction. Infiltrations were formed both at the site of the previous mercurial injections as well as at the site of the new injection. 2. By vigourous massage of the site of injection a rise of temperature up to 102.2° F. may still

be produced one week after the injection. This phenomenon may be explained by the more active absorption of the preparation resulting from the massage, or by the decomposition products of the tissues formed in the interval at the site of the injection.

Professor Dr. Maximilian von Zeissl: "Bericht über die Behandlung der ersten 100 Fälle mit Ehrlich 606" (*Wiener klinische Wochenschrift*, 1910, No. 38).

This author briefly summarizes the communications published by him regarding the effects of salvarsan. He emphasizes the fact that infiltrations were of rare occurrence in his cases.

Schreiber: "Ueber die intravenöse einspritzung des Ehrlichschen Mittels 606" (*Münchener medizinische Wochenschrift*, 1910, No. 39).

This author has demonstrated that the intravenous injection is innocuous when correctly administered, having treated over 325 cases with this method. It is essential that the preparation should be introduced into the circulation of the blood in a sufficiently diluted form; that is, in about 200 c.c. In his opinion it is advisable that the intravenous application should be rendered more effective by supplementing it with the intramuscular injection.

Dr. G. Hügel and Dr. A. Ruete: "Unsere bisherigen Erfahrungen mit den Ehrlich-Hataschen Arsenpräparat 606" (*Münchener medizinische Wochenschrift*, 1910, No. 39).

These authors comment favourably on the effect of the remedy as far as their observations, made to date, are concerned.

Josef Sellei (*Münchener medizinische Wochenschrift*, 1910, No. 39).

Sellei studied eighty-six cases but was unable to report any success in tabes and paralysis.

In Nos. 37, 38, 39, and 45 (1910) of the *Medizinische Klinik*, answers to inquiries in regard to experiences with salvarsan were published, of which we quote the following:

Name	Dose and Technique	Result	Recurrence	By-Effects	Wassermann Reaction
Grouven (Halle)	Largest dose 1.2 gm. At first alkaline solution, then neutral suspension.	Thus far favourable, especially when preceded by mercurial treatment.	Thus far in two cases, but time of observation was too short to decide this question definitely.	Local pain and infiltrations, slight temperature elevations often, high temperature rarely, toxic exanthem, weakness, occasional dizziness.	Became negative slowly.
Schulz (Strassburg)	0.3-0.45 gm. in four cases, Alt method; in all later cases, Wechselmann-Lange method.	Almost always prompt success.	None observed.	Diarrhea in two cases, occasionally slight rise in temperature.	Not tested.
Aschaffenburg and Geissler (Lindenburg-Cologne)	0.6 gm. neutral suspension.	Five cases of brain syphilis, one success; the remainder not observed sufficient length of time. Three cases of paralysis, no visible results as yet.		Pain, slight motile disturbances in arm.	Negative in three cases after fourteen days.
Medizinische Klinik (Greifswald)	0.6 gm. neutral solution.	Cure.	None, so far.	Slight pain.	Still positive, after four to five weeks.
Clemenz (Chemnitz)	0.5 gm. intravenous.			Temperatures to 100° F.	

		Result	Recurrence	By-Effects	Wassermann Reaction
[illegible]	[illegible] gm. neutral emulsion	Favourable.	None, so far.	Local edema, erythema once, iris-exanthem.	Gradually becoming negative.
[illegible]	20 injections, usually 0.4–0.5 gm.	Almost always promptly in 2d & 3d stages. In 1st stage, not always absolutely cured.	Considerably less frequent than with mercury.	A few drug-eruptions, occasional skin necroses.	Generally favourably affected.
Leonor Michaelis (Berlin)	1 cgm. per kilo body-weight, in neutral suspension in 120 cases	Thus far, favourable result.	Thus far in 3 cases.	Pain, fever, infiltration.	Frequently changed to negative, but not always.
Kromayer (Berlin)	0.3–0.5 gm. At first neutral, later paraffine emulsion.	The dose was not always effective.	Thus far 4 times in 160 cases.	Several times vomiting, rise in temperature and discomfort.	Changed to negative in 50%.
Edmund Saalfeld (Berlin)	0.6 gm. Leonor Michaelis method, with slight modification.	Generally favourable.	None, so far.	Painful infiltrate, multiform erythema once.	
Halberstaedter (Berlin)	0.6–0.7 gm., subcutaneously, in neutral suspension, Wechselmann-Lange method.	Always favourable, except in one case.	One, thus far.	Once exudative multiform erythema and joint swelling otherwise infiltrate, pain, palpitation of heart.	

C. Bruhns (Berlin)	0.45–0.6 gm. neutral emulsion, Wechselmann-Lange.	Slow, satisfactory result in the cases observed.	2 cases after 6 weeks.	Slight temperatures and pains, passing palpitation and diarrheas.	Usually remained positive.
Jadassohn (Berne)	0.6 gm., mostly Michaelis method.	Prompt and favourable, except in one case.	None observed.	Pain.	Still positive, one primary case became negative.
Karl Herxheimer (Frankfurt on Main)	0.6 gm. neutral emulsion.	Favourable.	2 local, in 230 cases, up to August 30, 1910.	Fever and infiltrate.	Negative in 75% after 50 days.
Luiser (Tübingen)	0.3 to 0.8 gm. in methyl alcohol and physiologic NaCl solution.	Cure or improvement.	In several cases, often as early as 4 to 6 weeks.	Pain, seldom temperature elevation.	Negative in 60 to 70%.
Bering (Kiel)	0.08 gm. per kilo body-weight, intragluteal, neutral suspension.	Most favourable in 2d and 3d stages.	4 times after 3 to 4 weeks; majority occurred in primary stage.	Infiltrate, pain, temperature to 104° F. Two arsenic enanthemata, 1 gangrene, 2 abscesses, 4 albuminuriæ, 1 detrusor paralysis, rectal tenesmus, diabetes aggravated.	Became negative in 26 cases, remained positive in 40 cases.
A. Cramer (Göttingen)	0.5 gm. Alt and Wechselmann-Lange.			Slight rise in temperature.	Negative 8 to 14 days after injection.

Name	Dose and Technique	Result	Recurrence	By-Effects	Wassermann Reaction
Spiethoff (Jena)	0.7 gm., the maximum dose, in emulsion.	Favourable, so far; improvement of general condition.	Attributes recurrence after 3½ weeks to insufficient dosage.		With larger doses, it became negative sooner.
Felix Pinkus (Berlin)	0.4 to 1.1 gm.; acid solution 10, neutral 17, alkaline solution 3 times.	Favourable.	Time too short—since July 6, 1910.	Fever to 102° F. Necrosis 3 times with alkaline solution, toxic exanthem once, icterus catarrhalis once, diarrhea once.	Became negative in primary stage, but not yet in secondary.
Kurt Brandenburg (Gr. Lichterfelde)	0.5 gm. neutral suspension, intramuscular.	Surprisingly rapid as against mercury, and general improvement.		Fever, infiltrate, pain.	Twice negative after 14 days, remained positive twice after 3 weeks.
Rille (Leipzig)	Over 100 cases, neutral or faintly alkaline, with methyl alcohol.	Generally cured within 7 to 34 days.	Thus far one case after four weeks.	Erythema, 9 times, vomiting and dizziness, weakness in the limbs, 8 times, icterus twice, 1 epileptic attack, pain and dyspnea.	Remained positive in most cases; became negative in five cases.
Wolters (Rostock i. M.)	0.4–0.5 gm. Wechselmann - Lange, subcutaneously.	Very successful.	None thus far.	Occasional temperature rise and general excitability.	Seems to become negative after 4 to 6 weeks.

Buschke (Berlin)	0.3–0.4 gm. in six cases.	One failure, which also did not respond to Hg or KI. 5 cures after 2–3 injections of salicylate of Hg and KI.		Fever lasting several days, twice pain and slight symptoms of arsenic intoxication.	
G. Treupel (Frankfurt on Main)	Dosis tolerata = 1.0 gm. Alt solution, Wechselmann suspension and Blaschko neutral suspension.	Successful in all cases except in paralysis.	Thus far none, after six months' observation.	Infiltrate in every case lasting weeks.	Becomes negative in most cases in 40 to 60 days.
Max von Zeissl (Vienna)	0.5 gm., after Ehrlich's original method.	Successful in all the cases.	Thus far none—observation from July 7th to September 7th.	Pain, twice headache and vomiting, rarely infiltration.	In most cases it became negative.
Walter Pick (Vienna)	Maximum dose 0.7 gm. Blaschko neutral suspension.	Generally favourable.	Four cases.	None, except pain.	Became negative in 2 to 6 weeks.
Weber (Berlin, White Sea)	At first, weakly acid solution according to Alt, then neutral or weakly alkaline, always intragluteal.	Always successful.	2 slight cases (dose 0.3 gm.) disappeared after reinjection.	Temperature rise in first 24–30 hours, moderate pain in buttocks up to 4 days.	Always became negative within 14 to 41 days.

Name	Dose and Technique	Result	Recurrence	By-Effects	Wassermann Reaction
Gennerich (Kiel-Wik)	Maximum dose, 0.5 gm. ntravenous, 0.7gm. subcutaneous. Intravenous (Schreiber), subcutaneous (Wechselmann), but not entirely neutralized.	Favourable, in 2d stage, especially after Hg treatment; very successful in cerebral syphilis.	3 cases in malignant syphilis, once in cerebral syphilis.	Pulse acceleration: in 72 cases, fever 4 cases, in one case duration more than one day. Pain with subcutaneous method, usually lasts 5 to 7 hours. With intravenous injection of 0.5 gm., macular arsenic eruption once, vomiting once, fever to 101° F.	In cases not treated with Hg, reaction became negative in 4 to 5 weeks; more rapidly after reinjection or Hg treatment. Cases first treated with Hg become negative quickly. Comparative recession of the reaction to same degree as clinical course of disease; often reaction changes to positive in the beginning.
Scholz (Königsberg)	0.6 to 0.7 gm. methods of Michaelis, Alt and Wechselmann.	Mostly favourable, especially in tertiary syphilis, and in cases resistant to mercury.	4 cases, with doses of 0.3–0.4 gm.	Quite severe pain with Michaelis and Alt methods; uneven absorption with Wechselmann method.	Remained positive usually after five to six weeks.

H. Schlesinger (Vienna)	0.3-0.6 gm., at first according to Ehrlich, later after Wechselmann.	Successful in 2 cases of multiple osteoarthritis, with high fever; in several cases of luetic meningomyelitis; no success in degenerative diseases of the central nervous system or in gummatous meningeal processes situated at the base.		Almost regularly sacral edema, pulse acceleration and diminished blood-pressure; also diminished amount of urine in the first weeks. In almost 50%, transitory albuminuria, or casts without albumin. Occasionally passing bladder disturbances; in one case high fever lasting three weeks (no local infection). In a young girl, with aortic insufficiency, a severe attack of angina pectoris.	In most cases remained positive after two to ten weeks.
Schreiber (Magdeburg)	Maximum dose, 0.7 gm. intramuscular; 0.5 gm. intravenous. At first in alkaline solution, at present intravenous method.	Favourable, especially in late lesions.	16 cases, with doses of 0.3 to 0.4 gm., one case with a dose of 0.7 gm. Since June, no recurrence thus far, with intravenous method.	With the intramuscular method, much pain, accompanying infiltration and fever. With the intravenous method, fever in recent cases only, or in late tertiary types; sometimes vomiting or diarrhea.	About 50% of cases became negative after the first injection.

Name	Dose and Technique	Result	Recurrence	By-Effects	Wassermann Reaction
Robt. Duhot (Brussels)	Maximum dose 1.1 gm. intramuscular, 1. gm. intravenous.	Favourable, especially in tertiary lues and tabes.	One case, with a dose of 0.3 gm.	Rather severe pain, 5 times quickly passing exanthem, 3 times bloody expectoration.	In 2 cases of chancre, reaction became negative on second day; in 2 cases of 2° lues, became negative on 20th day.
Géronne (Wiesbaden)	0.8-0.9 gm. both intravenous and intramuscular. 220 intravenous injections of alkaline solution; 40 intramuscular or subcutaneous, first after Alt, then after Wechselmann, now after Kromayer.	Successful in most cases, especially in late types.	14 cases out of 80, of which 11 in the same place, 3 elsewhere.	Severe pain with Alt and Wechselmann methods, less pain with Kromayer method. After intravenous method, temperature rise (100°-102° F.), occasionally vomiting and slight albuminuria.	Of 77 cases, 37 became negative, 40 remained positive. Of these 13 were reinjected, of which nine became negative.
Deneke (Hamburg)	All methods tried, but Blaschko's the last, being best tolerated.	Rather favourable in 1st and 2d stages; not very successful in 3d stage; no success whatever in metasyphilitic diseases.	One case, in precocious tertiary ulcerative process in pharynx.	Once, detrusor paralysis in cerebrospinal lues, improvement in a few days.	Cannot be decided thus far.

Ledermann (Berlin)	Maximum dose, 0.6 gm. 8 injections after first Wechselmann method, 26 subcutaneous in neutral suspension near scapula.	Mostly successful; in one case of primary lesion, after 0.3 gm., roseola appeared after 14 days. No result in metasyphilis.	Four cases.	Insomnia, tachycardia, slow pulse, radiating pain, especially after intramuscular injection; sometimes rise in temperature.	2 cases out of 34 became negative. Most cases not observed long enough.
Zumsteeg (Berlin)	Maximum dose, 0.8 gm., Wechselmann method.	Successful in 3 cases out of 4 cases of secondary lues; doubtful in one case because of complicating tuberculosis		One case rise of temperature lasting one day.	Remained positive
Chrelitzer (Posen)	Maximum dose, 0.6 gm., Wechselmann's neutral emulsion.	Favourable.	None, thus far.	Some pain at site of injection, occasionally infiltration lasting some time, pain usually passing off after five days.	Still positive after four weeks.

Name	Number of Cases Treated	Recurrence	Size of Dose Given in Recurring Cases	Remarks
Jadassohn (Berne)	82 cases, up to October 24, 1910.	3 cases.	1. 0.5 gm. Michaelis method. 6 weeks later, mucous patches returned. 2. 0.6 gm. neutral suspension. 3. 0.6 gm. Michaelis method.	1. 2. Five weeks later, patches returned. 3. Doubtful, as new papular foci appeared, while the old ones were still in process of healing, and then receded without treatment.
Karl Herxheimer (Frankfurt on Main)	789 cases.	33 cases.		Of the cases treated 100 not observed long enough, 150 cases of latent syphilis; therefore impossible to state percentage of recurrence.
Spiethoff (Jena)	175 cases.	5 cases.	1. 0.3 gm. 2. 0.6 gm. and 4 weeks later 0.4 gm. 3. 0.6 gm. 4. 0.3 gm. 5. 0.45 gm.	1. Primary lesion. After 4 weeks, extensive papular syphilide, then 0.5 gm. and 8 weeks later, plaques on mucous membrane. 2. Roseola. Seven weeks later, papules on genitals. 3. Papulo-pustular syphilide. Three weeks later new eruption. 4. Diffuse roseola. Three weeks later headache and plaques. 5. Primary lesion. Eight weeks later luetic facial paralysis.

Luiser (Tübingen)	80 cases.	4 cases.	0.3 gm.	Case 1, primary; case 2, secondary; cases 3 and 4, tertiary lues. Result of reinjection, performed in 3 of these cases, still in doubt.
Bering (Kiel)	285 cases, of which 211 were reexamined.	25 failures.	0.3 gm. 6 times.	4 cases of secondary, 1 case of tertiary, 1 case of congenital lues.
			0.35 " 4 "	4 cases of secondary.
			0.4 " 3 "	2 cases of secondary, 1 case of tertiary.
			0.45 " 1 time.	1 case of tertiary.
			0.5 " 3 times.	3 cases of secondary.
			0.55 " 1 time.	1 case of tertiary.
			0.6 " 1 "	1 case of secondary.
			0.75 " 1 "	1 case of secondary.
			0.8 " 5 times.	5 cases of metasyphilis.
Pinkus (Berlin)	120 cases.	3 cases.	0.6 gm. once. 0.65 " twice. 0.7 " three cases.	
Rille (Leipzig)	171 cases.	7 cases.	0.4 gm. 2 cases.	Men.
			0.45 " 3 "	Women.
			0.7 " 5 "	Men.
Wolters (Rostock)	35 cases.	None.		

Name	Number of Cases Treated	Recurrence	Size of Dose Given in Recurring Cases	Remarks
Treupel (Frankfort on Main)	120 cases.	4 cases.	0.6 gm. (Wechselmann) 3 cases. 1.0 gm. (Blaschko) 1 case.	
Juliusberg (Posen)	55 cases	2 recurrences or failures, as healing is incomplete.		
Grouven (Halle)	254 cases, of which 180 had veritable clinical symptoms.	(*a*) 15 failures; symptoms wavered or incompletely disappeared. (*b*) 9 recurrences.	(*a*) Case Dose 1. 0.6 2. 0.5 + 0.3 3. 0.6 + 0.3 4. 0.6 + 0.5 5. 0.7 + 0.5 6. 0.6 + 0.3 7. 0.4 + 0.7 + 0.6 8. 0.4 + 0.6 9. 0.5 10. 0.4 + 0.9 11. 0.6 + 0.3 12. 0.5 + 0.4 13. 0.6 14. 0.3 + 0.6 + 0.7 15. 0.3 + 0.6 + 0.7 (*b*) Case Dose 1. 0.5 2. 0.5 + 0.3 3. 0.8 4. 0.6 5. 0.3 + 0.6 6. 0.3 7. 0.5 8. 0.1 9. 0.05	(*b*) Cases 8 and 9 refer to children with hereditary lues. Wassermann reaction became negative or weakly positive in 29 cases; in 8 of these cases, traces of symptoms or recurrences are still to be seen.
Bettmann (Heidelberg)	87 cases	8 cases.	0.5 gm. 1 case. 0.6 " 7 cases.	

Schulz (Strassburg)	28 cases.	1 case.	0.3 gm. alkaline solution, intramuscular.	Patient was injected July 16, 1910, and at present has roseola again on the trunk.
Clemens (Chemnitz)	4 cases (intravenous).	None.		Eight weeks has been the longest period since the injections; one case of tertiary skin lesions, the rest, metasyphilitic. Good result in paralysis; good symptomatic result in tabes; in one case, lower temperature in the child of a wet nurse suspected of syphilis, and who was injected; Wassermann reaction + + +.
J. E. R. McDonagh (London)	85 cases.	2 cases.	0.4 gm.	The recurring cases later received 0.5 gm. but did not completely recover. The first dose should be 0.6 to 0.8 gm.
Wechselmann (Berlin)	1,250 cases.	About 40 cases.		The number of recurrences is of no significance, as but a small percentage of the cases treated have returned.
L. Michaelis (Berlin)	169 cases, of which 120 purely syphilitic.	3 cases.	0.3 gm.	Recurrence appeared 2 to 3 months after the injection.
Kromayer (Berlin)	310 cases.	7 cases.	0.3 gm. 5 cases. 0.7 " 1 case. 0.8 " 1 "	Most of the cases have not been under observation long enough to report on recurrence.

Name	Number of Cases Treated	Recurrence	Size of Dose Given in Recurring Cases	Remarks
Saalfeld (Berlin)	36 cases.	5 cases.	0.45 gm. 2 cases. 0.5 " 3 "	
Halberstädter (Berlin)	55 cases	6 cases.	0.02 gm. 1 case. 0.1 " 1 " 0.3 " 1 " 0.5 " 1 " 0.5 " 1 " 0.6 " 1 "	1. A nursing infant. 2. Child four years old. 3. Adult. 4. " 5. " 6. "
Ledermann (Berlin)	52 cases.	6 cases.	0.3 gm. 1 case. 0.4 " 1 " 0.45 " 1 " 0.5 " 1 " 0.6 " 1 "	Roseola, 2 cases; papular exanthem, 2 cases; mucous plaques, 1 case; periostitis, 1 case.
Chrzelitzer (Posen)	47 cases.	1 case.	0.5 gm.	
W. Scholz (Königsberg)	130 cases.	5 cases.	0.3 gm. 2 cases. 0.4 " 2 " 0.5 " 1 case.	
Schlesinger (Vienna)	21 cases.	None.		None but late syphilis and metasyphilitic affections were treated.
Schreiber (Magdeburg)	(*a*) 152 cases intramuscular. (*b*) 565 cases intravenous.	(*a*) 18 cases. (*b*) 1 case.	(*a*) 0.3–0.4 gm. 17 cases. 0.7 gm. 1 case.	Case *b*.—The patient was requested to submit to a reinjection after 4 weeks, the Wassermann reaction still being positive, but he refused a second injection.

Dr. Gennerich, Staff Surgeon, H. M. Navy, Chief Surgeon of the Marine Hospital in Kiel-Wik (same number):

1. Eighty-two cases were treated.

2. In the first malignant case recurrence took place three times. The first time, twenty-five days after 0.3 gm. salvarsan. After the second dose, i.e., 0.5 gm., the patient did not improve in spite of simultaneous treatment with calomel. For that reason the third dose was administered thirty-one days later, as a result of which cicatrization took place. Fourteen days thereafter the patient again was very weak, stating that he felt that a return of the disease was imminent. As a matter of fact, on examination new papules were found at the site of the old ulcerations and a little below and also a slight membranous coating on the left tonsil. Therefore an intravenous application of 0.5 gm. was administered on the fifteenth day and four days later a subcutaneous injection of 0.5 gm. Healing took place promptly. General condition was excellent and the patient who had been badly run down recuperated splendidly. This successful outcome has thus continued for nearly three weeks; and I therefore assume, in view of the briefly effective period of the preceding injections, that we have at last conquered the infection.

In the second malignant case (syphilis of the throat), recurrence appeared after 0.5 gm. salvarsan. This might possibly have been avoided if the treatment had not been interrupted by the patient going to sea. The second injection, i.e., 0.6 gm., was administered five weeks after the first. At that time the healing of the ulcers and the line of demarcation were still very incomplete. Consequently an intravenous injection of 0.45 gm. was promptly administered fifteen days later and the process came to a standstill. The septum however, was nearly entirely destroyed.

The third malignant case corresponds somewhat with the last. A very severe case of throat syphilis having healed within ten days after an injection of 0.5 gm. salvarsan, decomposition of the nose and perforation of the hard palate occurred thirty days after the treatment was administered. The process was not brought to an end by a second injection of 0.5 gm. given thirty-four days after the first injection. Therefore an intravenous application of 0.4 gm. was administered ten days later and a subcutaneous injection of 0.5 gm. three days after that. Only then the ulcers began to clear up. The margin of the necrotic process of the septum was distinctly visible. It measured ½ c.m. in width and 2½ c.m. in length and ran parallel to the hard palate. On the tenth day however, the process made visible progress posteriorly. Thereupon an intravenous

injection of 0.5 gm. was administered on the eleventh day; this was followed by 0.6 gm. subcutaneously two days later. The diseased mucous membrane now began to desquamate rapidly. For the first time bleeding also set in, this being a very frequent occurrence during the healing of ulcerative processes after treatment with salvarsan. The malignant character of the affection now seems to have disappeared. In contrast with the preceding case, most of the septum has been preserved. The perforation of the palate is almost closed. Ten days later portions of the necrotic bone were easily removed. The necessity of the injections is made evident by comparison with the preceding case. In a previous communication it has already been stated that calomel treatment, even carried up to the point of salivation, was not able to prevent the first relapse.

In the fourth case the right arm and leg were paralyzed, likewise the face and tongue on the left side, evidently through an obliterating endarteritis in the region of the inner capsule. After 0.6 gm. had been administered the paralysis diminished with surprising rapidity. Towards the end of the fourth week, the gait again became spastic; severe headaches also appeared which promptly improved after another injection of 0.5 gm.

From the course pursued by these cases I have arrived at the conclusion that the pathologic phenomena can be overcome when proper doses of the preparation are administered and particularly by a combination of the intravenous with the subcutaneous injections.

Dr. Géronne, Municipal Hospital, Wiesbaden (same number):

"To date we have treated approximately 300 patients with salvarsan. About 250 were syphilitic—primary, secondary and tertiary degrees. About fifty patients were suffering from metasyphilitic affections of the visceral organs and particularly of the nervous system.

"In the 250 syphilitics thus far treated we have observed clinical recurrence in twenty-eight cases. We have also administered reinjections of salvarsan to some thirty-six patients. In these cases the first injection did not influence the Wassermann reaction in respect of its not having changed to negative, or after having become negative in not remaining so.

"As the figures just given do not contain anything to show the accuracy of these observations and above all nothing in regard to their duration, it goes without saying that a compilation cannot convey a correct idea of the frequency of recurrence in the treatment of syphilis with salvarsan. To decide this question it will be necessary to consider only such cases as have been under close control for a considerable time, at least three months. Eliminating all other cases, we are at present in a position to report from

our records on seventy-one luetics treated with salvarsan from April to July, under the most precise clinical and serological observations. Among these patients clinical recurrence was observed in twenty-two cases. Twenty-four were reinjected because the Wassermann reaction remained positive and it is possible that a large proportion of clinical recurrence that might have taken place has thereby been prevented.

"In the cases under consideration there were sixty cases of secondary and tertiary syphilis in which recurrence took place seventeen times and eleven primary affections with five recurrences. In the primary cases recurrence appeared *in situ* (reinduration) four times and general recurrence (roseola and angina) but once. Furthermore in two primary cases the slightly positive Wassermann reaction became stronger and remained positive in spite of two or three additional injections of salvarsan. Four of our primary cases have thus far remained well clinically and in these instances the Wassermann reaction did not become positive. The period of observation has been five or six months.

"If the data in these our first cases do not seem to be favourable, we may attribute the result at least in part to the fact that we were using much smaller doses at that time than we do at present. For some time we have been employing larger doses in combination; that is, the intravenous with the alkaline intramuscular injection, or with the neutral suspension subcutaneously. In our earliest cases we injected smaller quantities of the substance in solution; twenty-one patients were treated with the alkaline solution according to Alt and fifty received the intravenous injection alone.

"As to the dosage, the twenty-two cases of recurrence were divided as follows:

Four cases were given 0.3 gm. intramuscularly according to Alt.
Nine cases were given 0.3 gm. intravenously.
Six cases were given 0.4 gm. "
Two cases were given 0.5 gm. "
One case was given 0.6 gm. "

"Basing our judgment on our present experience, we should not expect too much of the remedy as far as its permanent effect is concerned. Even with our large doses of 0.7 to 1.0 gm., and with the combined intravenous and intramuscular applications, we have seen recurrence in six cases in spite of the brief period of observation that has thus far elapsed; and we may add that notwithstanding the large dosage, the effect upon the

Wassermann reaction has not been any more favourable. Therefore we are of the opinion that in most cases a combination of salvarsan with mercury and iodide of potassium will be required to give our syphilitic patients the most favourable chance to obtain a permanent cure."

Treupel reports (*Deutsche medizinische Wochenschrift*, No. 39, September 29, 1910) in regard to additional experience with syphilitic, para- and metasyphilitic affections in which salvarsan has been administered. The various methods of injection were tested in seventy cases. It was shown that the best methods of administration were the subcutaneous neutral injections and the intravenous applications when a rapid effect was needed, as in cerebral lues with threatening symptoms of paralysis of the vital centres. Treupel once observed necrosis after a subcutaneous injection. In Treupel's laboratory Beisele has studied the problem of producing indefinitely stable solutions of salvarsan. He found that the substance is soluble in solutions of grape sugar of varying concentration and that these solutions will retain their effectiveness for some length of time. The grape-sugar solution may then be mixed with sodium hydroxide almost to the point of neutralization without causing precipitation. He also found that concentrated grape-sugar solutions will prevent oxidation of the preparation. As to the practicability of applying this method however, the author does not make any statement.

Among the cases treated there were patients with grave lesions of the cardiac muscle and coronary sclerosis and also with aneurysmal dilatation of the aorta, all of whom tolerated the injection quite well. Pulmonary tuberculosis, diabetes mellitus and nephritis are not considered a contraindication. In a case of gravest parenchymatous nephritis with incipient uremia, 0.6 gm. salvarsan was administered subcutaneously and several weeks later 0.4 gm. The uremic symptoms promptly receded after the first injection and they have not yet returned. The albumin in the urine first decreased from nine-tenths per cent. to two-tenths per cent., but when the patient was discharged it had again increased to six-tenths per cent.

In recent cerebral syphilis a particularly gratifying result was noted. Paralytic symptoms and beginning choked disc receded rapidly. In a case in which infection had occurred two years previously, complete paralysis of the right side of the body, ataxia and the Romberg symptom disappeared fourteen days after the injection. Gait and muscular strength again became normal and papillitis on the left side passed off.

In another patient with spastic paralysis of the legs and slight disturbances of the bladder, who was infected five years ago and who was treated

with mercury without success, the marked tendency towards spasms was considerably diminished.

At any rate, it is Treupel's impression that incipient tabes and very early progressive paralysis are favourably influenced by the treatment. The disturbances of sensation in tabes were diminished during the first weeks after injection, walking became steadier and the Romberg symptom either disappeared or was considerably reduced. In paralysis an enhanced psychic equilibrium seemed to be attained as regards all the mental functions.

In a case of tabo-paralysis without actual derangement of the bladder, the patient nevertheless frequently tried to empty her bladder as she feared she would wet herself unconsciously. She stated after the treatment that she was again able to determine the degree of fulness of her bladder at any given time.

Pasini: Corriere sanitario, 1910, No. 30.

Micheli and Quarelli: Corriere sanitario, 1910, No. 30.

Fauser: Med. Korresp.-Bl. d. württemb. ärztl. Landesv., Juli, 1910.

Igersheimer: Berliner klin. Wochenschrift, 1910, No. 33.

Meltzer: New York Medical Journal, 92, No. 8.

Bertarelli, Pasini, Bottelli: Giornale italiano delle Malattie Veneree e della pelle, 1910, No. IV.

Wicherkiewicz: Przeglad Lekarski, 1910, No. 34.

Nocht and Werner: Deutsche medizinische Wochenschrift, 1910, No. 34. Malaria.

Meilian: Le progrès medical, 1910, No. 35.

Heubner: Therapeutische Monatshefte, 1910, Heft 8.

Basch: Budapesti Orvosi Ujsag, 1910, No. 37.

Ehrmann: Wiener medizinische Wochenschrift, 1910, No. 38.

Fuld: Semaine médicale, 1910, No. 39.

Kalb: Wiener klinische Wochenschrift, 1910, No. 39.

v. Torday: Wiener klinische Wochenschrift, 1910, No. 39.

Marsori: Gazzetta internationale de Medecina, etc., 1910, No. 39.

Werner: Deutsche medizinische Wochenschrift, 1910, No. 39. Malaria.

Murphy: Journal of American Medical Association, 1910, No. 13.

Forbat: Wiener medizinische Wochenschrift, 1910, No. 40.

Wechselmann: The Treatment of Syphilis with Ehrlich's Dioxydiamidoarsenobenzol (New York Medical Journal, 3. IX. 1910).

Wechselmann: The Treatment of Syphilis with Ehrlich's Dioxydiamidoarsenobenzol (The Lancet, 29. X. 1910).

Fritz Lesser: Organotrop—Spirillotrop (Berliner klinische Wochenschrift, 1910, No. 43).

Wechselmann: Latest Personal Experiences with the Ehrlich-Hata Remedy (606) in the Treatment of Syphilis (Interstate Medical Journal, St. Louis, October, 1910).

Die Behandlung der Syphilis mit den Ehrlichschen Präparat 606. Verhandlungen auf der 82. Versammlung Deutscher Naturforscher und Ärzte in Königsberg, 20. IX. 1910 (Deutsche medizinische Wochenschrift, 1910, No. 41).

Campana: Un succedaneo del mercurio 606 (Riforma medica, XXVI, 38).

Pasini: Chemotherapia nella sifilide e il nuovo preparata di Ehrlich-Hata 606 (Corriere sanitario, XXI. 30).

The usual success in fourteen cases. The spirochetes disappeared in twenty-four to sixty-two hours; mouth spirilla and spirilla refringens were not affected. One patient injected April 28th with 0.3 gm. had a recurrence on June 8th.

Ritter: Erfahrungen mit dem Ehrlichschen Mittel 606 (Münchener medizinische Wochenschrift, 1910, No. 43).

Subcutaneous method better than intragluteal. Test the canula of the syringe, and take care not to inject into the cutis! Otherwise the well-known observations are confirmed.

Schwartz and Flemming: Beitrag zu den Untersuchungen über das Verhalten des Ehrlich-Hata-Präparates im Kaninchenkörper (Münchener medizinische Wochenschrift, 1910, No. 41).

Ehlers: Ehrlichs 606 gegen Lepra (same journal). Negative result.

v. Watraszewski: Beobachtung über die Wirkung des Dioxydiamidoarsenobenzol bei Syphilisformen (Allgemeine Medizinische Central-Zeitung, 1910, No. 44).

Hultgren: Om Behandlingen af Syphilis med. "Ehrlich-Hata" 606. Resebref. (Särtryck ur Hygiea, 1910).

Truffi: Il nuovo preparato arsenicale 606 di Ehrlich nella cura della sifilide (Biochimica e Terapia sperimentale. Anno II, Fasc. V).

The satisfactory results are confirmed. In most cases disappearance or loss of motility of spirochetes twelve to twenty-four hours after the injection. In three cases they were still motile on the fifth, sixth and eighth days respectively. Hyperleucocytosis, especially on the third and fourth days.

Favento: 156 mit Ehrlich-Hata 606 behandelte Fälle (Münchener medizinische Wochenschrift, 1910, No. 40, 4. X).

Schwartz and Flemming: Ueber das Verhalten des Ehrlich-Hataschen Präparates, des Arsenophenylglycin, des Jod-Kali und des Sublimat zur Wassermannschen Reaktion (Münchener medizinische Wochenschrift, 1910, No. 37, 13. IX).

All of these agents possess no hemolytic properties in any proportion of dilution, and can inhibit hemolysis only when very highly concentrated.

Duhot: "Le 606" (Annales de la Policlinique Centrale de Bruxelles, September 1910).

One hundred and eighty-five cases. Dose for healthy adults 1.0 gm. Points out the danger of hemoptysis in consumptives. After the intravenous injection of 1.0 gm. in one case, he saw a serious condition of marked oppression with vomiting, which lasted for ten minutes.

Ehrmann: Einige Bemerkungen über die Wirkung des neuen Ehrlichschen Präparates 606 (Wiener medizinische Wochenschrift, 1910, No. 38, September 17th).

The subcutaneous and intramuscular methods do not differ in effect and by-effects. Jarisch-Herxheimer also distinct in swelling of syphilitic foci. Salvarsan acts far more rapidly than mercury. Occasionally the symptoms recede rapidly in the beginning, then remain stationary.

Blaschko: Mitteil. d. D. Gesellsch. z. Bek. der Geschlechtskrankh., 1910, 8. Heft 4.

Blaschko: Kritische Bemerkungen zur Ehrlich-Hata-Behandlung (Berliner klinische Wochenschrift, 1910, No. 35).

Torday: Budapesti Orvosi Ujsag, 1910, No. 36.

McIntosh: The Lancet, February, 1910, No. 10.

McDonagh: (same journal).

Fleckseder: Wiener klinische Wochenschrift, 1910, No. 36.

Sellei: Gyógyáscat, 1910, No. 37.

Javaux: Presse Medicale Belge, 1910, No. 37.

Emery: La Préparation "606," Paris, 1910, Octave Doin et fils.

Malinowski: Przeglad Chorób Skornych i Wenerycznych, 1910, No. 8.

Nyström: Ehrlich-Hata-Meedlet, Stockholm, 1910, Bjork und Börjesson.

Truffi: Biochimica e Terapia sperimentale II, Heft 5.

Finger: Ärtzl. Reform-Ztg., 1910, No. 14.

SUMMARY

All of these observations are so much in accord regarding the favourable curative effect of the remedy in cases in which symptoms of syphilis are present and also in regard to its slight toxicity, that new developments in these respects may hardly be expected; it therefore appears to be superfluous to produce any further casuistic evidence. For this reason, the unfavourable opinions of Hoffmann and Buschke, being based upon very sparse observations, are rather surprising. It must be accepted as an established fact, that in Ehrlich's salvarsan we have an extraordinarily potent medium, far superior to the remedies heretofore used and in many serious cases an indispensable agent of specific anti-syphilitic effect. It must be distinctly emphasized that all authors, in spite of the startling and almost magic effects of the remedy, which have so aroused their enthusiasm, were determined in advance to remain uninfluenced by any illusions. They have at no time drawn positive conclusions as to an apparently complete cure of syphilis, but to the contrary, from the very beginning they have pointed to the fact that recurrence took place. It is therefore with the intention to mislead, that opponents again and again put forward questions that cannot be solved for a very long time in the very nature of things. These opponents generally harp on the word "cure," insinuating that it is being used in the literal sense, thereby sidetracking the discussion on a false basis and constituting for their own purpose as ingenuous an adversary as they require. The problem of the observer consists only in the calm and impartial study of one fact after another, without regard to what he may imagine as to the curative effect of the remedy. Only in this way will we be enabled in the future, to form an opinion as to actual cures, which we are at present still unable to do. Nevertheless, even to-day something may already be said within certain limits regarding the significance of the remedy in respect of the possibility of an actual cure of syphilis. The progress of syphilis cannot be foreseen in advance, and no one who is called upon to treat a syphilitic primary affection can safely guarantee the course that will be taken by the disease. But as opposed to the

intermittent method of therapy, which is based upon the probability of recurrence that often appears unexpectedly after intervals of years and decades, it should be pointed out that many cases of syphilis can without doubt be cured as a result of a single course of mercurial treatment. For instance, I have observed two cases which were treated with a single course of inunctions by Köbner and myself twenty-four and eighteen years ago respectively. There has never been any recurrence. Their wives and children are healthy and they show a negative Wassermann reaction.

It is not going too far to assume in such cases that one course of mercurial treatment has caused the destruction of all the spirochetes, and it is difficult to comprehend why the new remedy, with its spirocheticidal power admittedly far greater than that of mercury, should not more frequently produce a *sterilisatio magna.* After Ehrlich-Hata's experiments on animals, there can no longer be any doubt as to its capacity for destroying spirochetes.

At my request, Sieskind has made microscopic examinations of spirochetes after the injection of salvarsan, and his findings are as follows (*Dermatologische Zeitschrift,* XVII, 7, page 478):

Determination of Spirochetes in Patients Injected with Salvarsan

In thirteen cases we made a systematic investigation of spirochetes in patients to whom Ehrlich's salvarsan had been administered, using the dark ground illumination. We obtained the spirochetic material by irritating the secretion of papules located at the vulva, where experience has shown spirochetes are found in large numbers; also from the secretion of initial scleroses. As the subjoined table shows, we found that the spirochetes disappeared at the very latest, on the sixth or seventh day after the injection and in one case we failed to discover any spirochetes on the second day, in spite of very careful investigation. This disappearance of the spirochetes corresponded to the clinical diminution of syphilitic symptoms. In the cases in which the spirochetes disappeared rapidly we observed a distinct involution of the papules and scleroses within twenty-four hours. Therefore, it was no longer possible to determine the presence of spirochetes even after removing the superficial skin with the scalpel. In many cases the vital changes exhibited after the injection by the spirochetes, under dark ground illumination, are remarkable. The usual screwlike and oscillating motion of the spirochetes pallida is considerably decreased and frequently only slight movements are seen which

gradually cease entirely. In addition, not only their motility, but also their form is changed. The very spirochetes, which because of their frailty and slight refracting power have been surnamed "pallida," become bulky and swollen. Nevertheless, they retain their spiral form even in this condition of immotility. On the whole it would seem undeniable that Ehrlich's new arsenic preparation exerts a distinct, specific effect upon the spirochetes.

CASE 1.—Male. Primary infection on the lower lip. Injection, May 21, 1910, 0.4 gm. salvarsan.

Examination for spirochetes:

On May 17th, + +
" May 22d, + +
" May 23d, + } Spirochetes dentium, but no pallida
" May 24th, + }
" May 25th, + }
" May 26th, −
" May 27th, −

CASE 2.—Male. Primary lues, urethral chancre. Injection, May 27, 1910, 0.4 gm. salvarsan.

Spirochetes:

On May 25th, +
" May 28th, + } Changed in form and motility
" May 29th, + }
" May 30th, − }
" May 31st, −

CASE 3.—Male, primary and secondary lues. Chancre in coronary sulcus; moist papules on scrotum. Injection, June 1, 1910, 0.4 gm. salvarsan.

Spirochetes:

On May 30th, +
" June 1st, +
" June 2d, + Motionless
" June 3d, +
" June 6th, −
" June 7th, −

CASE 4.—Male, secondary lues, roseola. Injection, May 27, 1910, 0.4 gm. salvarsan.

Spirochetes:

On May 25th, + +
" May 28th, + Modified
" May 30th, −
" May 31st, −

CASE 5.—Male, secondary lues; roseola. Injection, May 30, 1910, 0.4 gm. salvarsan.

Spirochetes:

On May 28th, + +
" May 30th, +
" May 31st, −
" June 2d, −

CASE 6.—Female, secondary lues; groups of broad condylomata. Injection, May 25, 1910, 0.4 gm. salvarsan.

Spirochetes:

On May 24th, +
" May 25th, +
" May 26th, + } Modified in form and motility
" May 27th, + }
" May 28th, + }
" May 30th, + Motionless
" June 1st, −
" June 2d, −

CASE 7.—Female, secondary lues, papules. Injection, May 24, 1910, 0.45 gm. salvarsan.

Spirochetes:

On May 24th, +
" May 25th, +
" May 26th, −
" May 27th, −
" May 28th, −

CASE 8.—Female, primary lues, primary lesion. May 26, 1910, 0.45 gm. salvarsan.

Spirochetes:

On May 25th, +
" May 27th, +
" May 28th, +
" May 30th, + Motionless
" May 31st, −
" June 1st, −

CASE 9.—Female, secondary lues, papules. Injection, May 31, 1910, 0.4 gm. salvarsan.

Spirochetes:

On May 30th, + +
" May 31st, +
" June 1st, +
" June 2d, + Motionless
" June 4th, +
" June 6th, +
" June 7th, −
" June 8th, −

CASE 10.—Female, secondary lues; papules. Injection, May 24, 1910, 0.4 gm. salvarsan.

Spirochetes:

On May 25th, +
On May 26th, −
" May 27th, −
" May 28th, −

CASE 11.—Female, secondary lues; papules. Injection, May 27, 1910, 0.45 gm. salvarsan.

Spirochetes:

On May 27th, +
" May 28th, +
" May 30th, −
" May 31st, −

CASE 12.—Female, secondary lues; papules. Injection, May 30, 1910, 0.4 gm. salvarsan.

Spirochetes:

On May 30th, +
" June 1st, +
" June 2d, +
" June 3d, +
" June 4th, + Motionless
" June 6th, −
" June 7th, −

CASE 13.—Female, secondary lues; papules. Injection, June 9, 1910, 0.4 gm. salvarsan.

Spirochetes:

On June 8th, +
" June 9th, +
" June 10th, +
" June 11th, −
" June 13th, −

From a private communication made to me by Ehrlich it appears that similar observations were made previously by Ascoli, Truffi and Pasini.

These investigations dealt with injections of an acid solution. It has

often been stated that injections with a neutral emulsion were less effective. However, it is probable too, that when the dichlorhydrate is injected, precipitation occurs through the alkaline juices of the body, and it may be that salvarsan acts only in this form. We have not observed any difference clinically, nor have any differences been shown in previous investigations relating to the behaviour of the spirochetes. Sieskind investigated the following cases:

CASE 1.—Miss P. Ulcerated papules on the genitals; patches on the right tonsil. August 11th, spirochetes +. August 12th, injection 0.45 gm. salvarsan. August 13th, spirochetes −. August 14th, spirochetes −.

CASE 2.—Miss K. Plaques on tonsils; papules on genitals; edema of labia. August 12th, spirochetes + +. August 13th, injection 0.45 gm. salvarsan. August 14th, spirochetes +. August 15th, numerous spirochetes, mostly modified, some of them barely alive. August 16th, spirochetes −.

CASE 3.—Miss W. Plaques on tonsils, confluent ulcerated papules. August 11th, spirochetes +. August 12th, injection 0.45 gm. salvarsan. August 13th, spirochetes +. August 14th, spirochetes −. August 15th, spirochetes −.

CASE 4.—Miss F. Ulcerated papules of the genitals; papules on the tongue; ulcerations of the palatal arches; papules of the corners of the mouth; ulcerated papules of the toes. August 26th, spirochetes + +. August 27th, injection 0.45 gm. salvarsan. August 28th, isolated, motionless and swollen spirochetes. August 29th, spirochetes −.

CASE 5.—Fritz Z. Primary lesion of the lower lip. August 30th, spirochetes + + (definitely recognized as pallida). August 30th, injection 0.6 gm. salvarsan. August 31st, spirochetes motionless, dead. September 1st, spirochetes −.

CASE 6.—Miss P. Ulcerated papules of genitals; macular exanthem. August 11th, spirochetes +. August 12th, injection 0.45 gm. salvarsan. August 13th, spirochetes −. August 14th, spirochetes −.

From the six cases just mentioned, it may be assumed that the statement made by Neisser, Hoffmann and Alt, to the effect that the spirochetes are not made to disappear as rapidly by the subcutaneous injection of the emulsion, is not correct. In numerous other cases Sieskind also generally found a decrease of motility and a change of form within twenty-four hours after the injection and complete disappearance of spirochetes within forty-eight hours.

In the cases of two children who died two and four days after the injection respectively, Herxheimer (Wiesbaden) and Reinke (*Deutsche medizinische Wochenschrift*, No. 39) investigated the organs according to

Levaditi, without finding any spirochetes, except in the lungs, where a few degenerated specimens were present. They were swollen, devoid of their spiral curves, agglutinated and partly decomposed. We also found a similar result in four children. In one of these the liver, kidneys, lungs and intestines were investigated, many sections having been prepared. In the others, the spleen, suprarenals and heart were also investigated in the same way.

CASE 1.—This was a child suffering from a most aggravated form of syphilitic pemphigus, the patient's condition being exceedingly poor. It weighed but 62.2 ounces and it was necessary to keep it in an incubator. The disease had progressed to such an extent that one of the nostrils was destroyed and the terminal phalanges of the child's fingers had become gangrenous. On June 23d, the child was given 0.015 gm. salvarsan. The syphilitic symptoms on the skin disappeared very rapidly, but the child died on July 2d. The post-mortem examination revealed multiple broncho-pneumonic foci, pulmonary abscesses of various sizes, acute parenchymatous nephritis, the spleen and liver greatly enlarged, deep luetic ulcerations in the large intestine, with abnormal growths and the formation of stenoses in several places.

According to all experiences, even if the occasional unreliability of Levaditi's method is taken into account, the presence of spirochetes should be expected in such a case, but none was found in any of the organs. This finding also applies to the other cases.

CASE 2.—Waldemar v. D., aged five months. Tuberculo-papular syphilides all over the body, ulcerations the size of a dime on the mento-labial fold. Coryza, specific rhagades on the lips. Spirochetes found with dark ground illumination. On March 15th, 0.033 gm. salvarsan was given. On March 16th, distinct decrease of the tuberculo-papular syphilides; onset of characteristic meningitic carriage of the head; spasms of upper and lower extremities; pupils reacting. When its head was held up the child gave signs of suffering pain. The temperature, which was 102° F. previous to the injection, rose to 104° F. Congestion in the lower lobes of the lungs. On March 17th, spirochetes +; urine free from albumin. During the next few days the symptoms receded a little, but on March 23d, death occurred.

Post mortem: Pneumonia, multiple gummata in the muscle of the heart, specific osteochondritis. No pathologic symptoms observed in the other organs.

With Levaditi's method, no spirochetes were found in any of the organs.

CASE 3.—Charlotte P., born May 6, 1910. *Status*, July 25, 1910: Deep ulcerations on the face, particularly near the nose and about the mouth and eye-

lids; deep ulcerations on the trunk; the skin is pustular and desquamating in layers; very severe coryza; inguinal adenitis. On July 26th, 0.03 gm. salvarsan. July 27th, temperature 104° F. On July 29th, death. The case was hopeless from the beginning. Post-mortem examination showed the above-mentioned changes of the skin throughout the entire body; syphilitic osteochondritis; the lungs contained air; the upper lobe presented a yellow gummatous tumour the size of a cherry, with a dense margin two mm. wide; kidneys turbid, with the

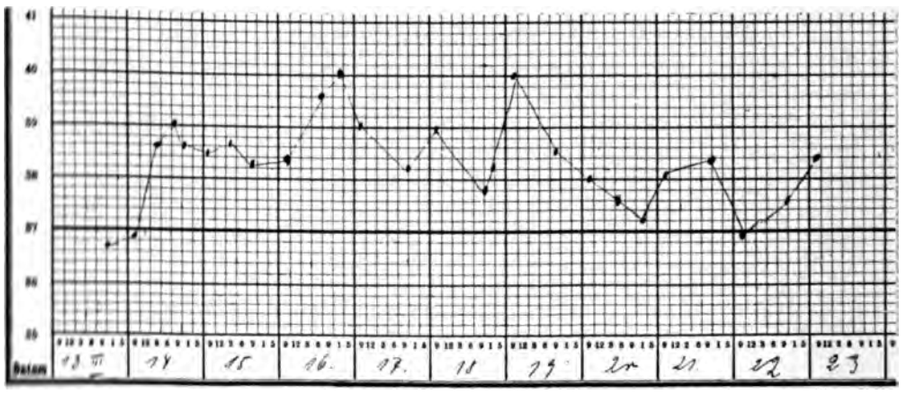


FIG. 9.

margins destroyed; cardiac muscle yellowish-red and turbid. Spirochetes were not found with Levaditi's method.

The same negative result was obtained in a fourth case.

CASE 4. Willy W., born April 24, 1910. Child of a luetic mother. No other data obtainable. Was taken ill with congenital lues, August 2d, 1910. *Status:* Well nourished suckling, well developed according to his age; constantly snuffling. Pulmonary: On the right side above the lower lobe, isolated, coarse rales are heard. Heart normal. Abdomen: spleen not palpable; the liver projects about two fingers above the costal arch. Skin: On the thigh and leg, isolated, circular, livid red macules are seen, some of them showing a macerated surface. The entire gluteal surface is in a macerated condition and also presents macular efflorescences the size of peas. The forearms and hands show a marked, scaly exanthem. Mucous membranes: The mucous membrane of the lips, particularly the lower and the adjacent skin, show numerous ulcerations covered with small crusts and diffuse syphilitic infiltration; the nasal mucous membrane is constantly secreting a catarrhal discharge; the corners of the eyes are also filled with a yellowish secretion. Glands, normal; genital organs, normal.

Optic nerve on both sides greyish-green discolouration, margin not well defined. Optic neuritis (Dr. Fehr). Wassermann reaction, + + +. On July 21st, 0.02 gm. salvarsan. July 26th, exanthem disappeared. July 28th, temperature 105° F. July 29th, normal. July 30th, ulcerations beginning to heal, temperature normal. July 31st, 98° F.; in the evening, 104° F. August 1st, 99° F.; in the evening, 101° F. On the evening of August 2d, death under constant rise of temperature.

Post-mortem examination: External and extremities: Corpse of a child fairly well nourished; little fat, skin flabby and yellowish. On the right side of the thorax anteriorly, an injection spot covered with adhesive plaster, also a small, yellow doughy mass in the subcutaneous tissue. Natural orifices of body normal. Epiphyses of femur normal. Thorax: Right pleural cavity filled with a greenish-yellow, thick fluid, covering the entire pleura, partly inspissated and adherent to it. Lungs: Both organs large, the upper lobe a fleshy red of usual consistency; right, middle, and both lower lobes rather bluish-red and of denser consistency; residual air in these portions increased. Blood and lymph contents normal. In the paler parts quantity of air normal, small quantity of blood, quantity of lymph somewhat increased. Isolated dense foci. Bronchi normal. Heart: Ventricle normal; myocardium pale; endocardium normal; valves and orifices intact. Aorta, normal. Abdominal cavity: Spleen large, dark black, reddish, tough; connective-tissue framework perceptible; capsule normal. Liver: Large, usual consistency, yellowish-red colour; surface normal; gall-bladder normal; pancreas normal. Stomach and intestines normal. Kidneys: Of usual size, surface smooth, cortex somewhat broadened, the markings not distinct; colour, brick red.

Anatomic diagnosis: Right empyema; double broncho-pneumonia; pulmonary hypostasis; cyanotic spleen; infiltrating fatty liver; parenchymatous nephritis.

If as above stated, the reliability of Levaditi's method cannot be assumed to be absolute, these negative results are nevertheless very surprising and remarkable, and they indicate, if confirmed by further investigations, that in isolated cases a *sterilisatio magna* may be possible.

On the other hand, it is equally certain that all the spirochetes are not always destroyed, for various reasons.

In the first place, the dose administered may be too small, or a dose sufficiently large may be absorbed too slowly, so that the concentration of the remedy in the fluids of the body is not sufficiently vigourous to destroy all the spirochetes. Up to the present moment, it has not been shown that there exists any striking difference in the therapeutic action of 0.5 gm., the dose recognized as being effective, and larger doses, up to 1.2 gm.; neither has any superiority for the intravenous method been demon-

strated. The method proposed in various quarters and recommended by Ehrlich himself, of quickly destroying the principal mass of the spirochetes by an intravenous injection, and attacking the remainder by a subcutaneous or an intramuscular deposit, has not yet been tried sufficiently.

But it may perhaps also be possible in this way to reach the remaining spirochetes, which from a biologic standpoint have been found to be the most resistant.

Arsenic-fast Strains Not Observed.—Inasmuch as it cannot be assumed that in an infection with syphilis various races of spirochetes thrive in the body at the same time, yet differing biologically in their behaviour toward medical agents, we may hope, through the preceding, to destroy the remaining spirochetes which have shown themselves the most obstinate to the treatment but not absolutely resistant. Up to the present, salvarsan-fast strains (not attacked by salvarsan) have not been observed with certainty. For in four cases, in which one injection had not the least effect on the symptoms which usually respond readily to the remedy, that is, two cases of plaques of the oral mucous membrane, roseola and slight papular exanthem, a successful result immediately followed a second injection. The following two cases may serve as an illustration:

Case 1.—Wilhelm S., was injected with 0.5 gm. salvarsan, on June 28th. He had plaques on the lower lip and tongue, and erosions on the penis. There was no distinct result. On July 23d, 0.5 gm. again injected. July 26th, plaques of lip healing, penis improved, tongue unchanged. August 3d, everything healed. August 16th, Wassermann reaction, ±. October 15th, completely cured.

Case 2.—Theodor S. Infected May 1, 1910. June 28th, roseola; 0.5 gm. salvarsan injected. July 7th, July 16th, July 29th, August 8th, roseola still present. August 8th, second injection of 0.5 gm. August 24th, almost healed, some isolated spots remaining as faint traces. September 13th, completely healed. October 14th, the same. Wassermann reaction, −.

Case 3.—Friedrich A. Infected in January 1910. Mercurial treatment. June 28th, roseola, plaques on right tonsil. July 22d, injection of 0.5 gm. July 29th, roseola pale; plaques still present. August 1st, again 0.5 gm. salvarsan; prompt effect. September 16th, almost cured. October 20th, completely cured. Wassermann reaction, −.

These instances in which the remedy fails to act, although as already shown in other cases, it is undoubtedly an effective preparation, can only be explained by the remedy being unable to reach the encapsulated foci of spirochetes. This attack is only possible when the tissue wall formed around the spirochetes (see below) has been sufficiently vascularized.

Therefore it appears that the effectiveness of salvarsan is rather augmented by a course of mercurial treatment given *before* the injection, as this according to all experience, exerts a favourable influence on the absorption of tissue. This seems to me to be indicated by the fact that in cases that have undergone mercurial treatment, recurrence has but very rarely taken place after treatment with salvarsan. On the other hand, mercury acts far less effectively on the symptoms remaining after the salvarsan treatment, than the new remedy, which exerts a far more energetic attack on the spirochetes. But after the first injection, such persistence of the remaining spirochetes does not seem to be present and this is made evident by the prompt action of the reinjections.

Sterilisatio Magna.—It must therefore be admitted that in many cases of syphilis a *sterilisatio magna* is possible and that it may be attained even by our present methods with which only a beginning has just been made, or by a better utilization of the curative powers of salvarsan. For other cases the hope is already justified that a repeated application of the remedy will produce a *sterilisatio fractionata.* This is established by the entire nature of the course taken by syphilis in the human body. The course of syphilis differs considerably from that of other protozoic diseases, particularly of the trypanosome in animals. Whereas in these diseases the parasites are reproduced in infinite numbers in the blood, thus ultimately bringing about the death of the host, these conditions never arise in human syphilis.

The spirochete pallida is not a blood parasite. It traverses through the blood-stream in large numbers but once in all probability. This has also been shown by the constantly negative results of the numerous examinations of blood that I have made in conjunction with Loewenthal and Canon; while the literature records but very few positive results, only isolated instances having been found even after the most careful investigation. After the spirochete has once traversed the blood-stream, it settles in the tissues. This localization takes place in disseminated foci. Every investigator of syphilitic organs that have been impregnated according to Levaditi's method, knows that the spirochetes are distributed throughout the organs in an apparently irregular manner, that hundreds of sections may be examined without any result and that nests are suddenly discovered containing innumerable spirochetes. Apart from the probable formation of anti-bodies, it is as a measure of defense on the part of the organism, that encapsulation of spirochetal foci is distinctly observed in the primary affection.

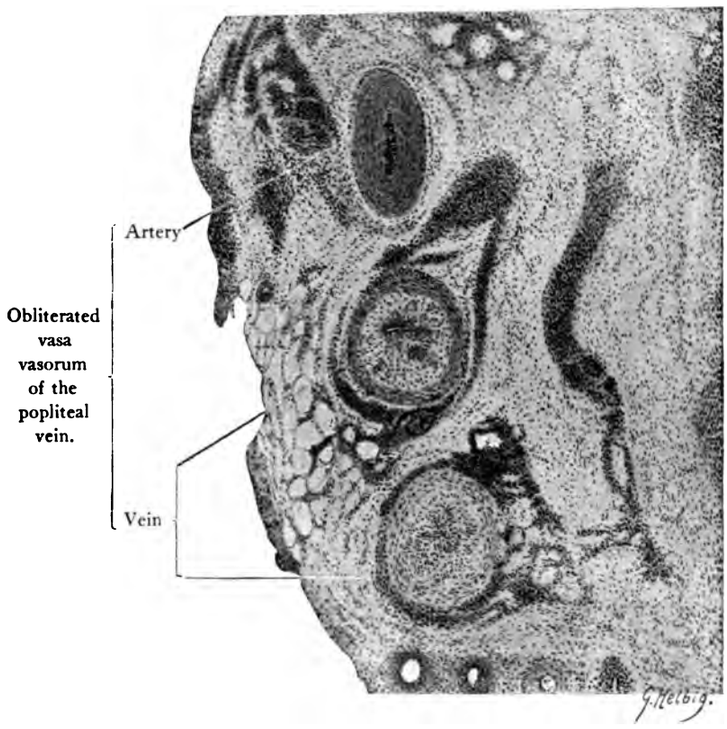
As a result of Ehrmann's classic investigations and wonderful injection preparations, we have learned a great deal concerning the course of syphilitic infiltrations in the body ("Zur Pathologie der Syphilitischen Initialsklerose des Penis." *Archiv für Dermatologie und Syphilis*, Bd. 68; also "Über die Peri- und Endolymphangitis syphilitica," same journal, Bd. 81). He has shown that they not only enter the lymph-channels, but still more important, that they travel along the lymphatic vessels or other preformed structures, nerves and muscles and also the connective-tissue spaces, the spirochete being a connective-tissue parasite. In these spaces, Ehrmann demonstrated, step by step, through all possible intermediate gradations, how a distinct encapsulation is formed from a loosely organized infiltration. A cell-growth takes place, accompanied by a repression of the connective-tissue cells which are crowded into the periphery of the nodules or focus thus being formed, in which elastic fibres predominate. Vascularization of the nodule is accomplished gradually. This infiltration moves towards the centre in the form of bands, thus giving expression to the advance of the spirochete in the connective tissue and thereby causing a corresponding reaction to take place. It not infrequently happens that a lymphatic vessel, the intima of which is quite intact, is entirely encompassed by such infiltrations. This condition may be readily explained. It is probable that the virus advances at this point along the lymphatic vessel and subsequently finds its way into the lumen, possibly at a point more nearly in the direction of the centre.

From this point the virus proceeds into the larger lymph-channels and subsequently into the lymph-channels that contain muscle fibres; it may still be possible however, that here also the virus travels through the connective-tissue spaces directly. The proliferation of the intima of the lymphatics and of its blood vessels, probably depends in part on the virus that is contained in the interior of the lymphatics. It also depends to some degree on the virus which finds its way through the small anastomotic vessels, which terminate in the substance of the intima some distance from the point of anastomosis with the principal lymphatics. Lastly it also depends upon the virus coursing through the connective-tissue spaces and also in the blood vessels which terminate there.

A number of investigators, principally Levaditi, Blaschko and others, have discovered that the spirochetes find lodgment in the connective-tissue spaces. They were seen by Scherber and Mucha in the interior of the lymphatic vessels of scleroses. Blaschko found them in a thrombus of the lymphatics and I also found quantities of them in a dense thrombus of an

inflammatory dorsal lymph-vessel. Wolters also found them in the thrombus of one of the veins of the penis, as shown in Hoffmann's atlas, Plate XVII.

However, Ehrmann's beautiful injection preparations show that part of these infiltrations which surround the spirochetal foci, are for a time (in the beginning) without any blood vessels. Later on, the small vessels



become infarcted and as a result involution processes follow, which are characteristic of syphilis. Furthermore the nutritive blood-capillaries which terminate in the extreme adventitious connective tissue are imbedded in infiltrations or obliterated by endovascular processes. This is beautifully demonstrated by the illustration on this page taken from a specimen of recent syphilis in the calf.

These conditions are of essential importance, particularly in the matter of secondary syphilis. But it is clearly evident however, that even

the most potent remedy cannot be effective, if it is unable to reach the spirochetes.

It is only when the process of organization and vascularization of these infiltrations and thrombi has progressed sufficiently that the spirochetes can be attacked by the remedy. For this reason it is my opinion also that the initial dose administered cannot play the same rôle with reference to the occurrence of relapses in syphilis as it does in trypanosome infection. In the latter we attain a *sterilisatio magna*, a complete cure, when we employ a sufficiently large dose of a remedy. But while the trypanosomes also disappear from the blood through a dosage insufficient for a complete cure, they reappear after a number of days and then again disappear temporarily after the further administration of larger doses. Ultimately no influence whatever is exerted by the remedy and as a consequence the death of the host is inevitable, because the remaining trypanosomes have become immune to the remedy as a result of the repeatedly insufficient dosage. In syphilis the case is different. J. Neumann has already demonstrated that in this disease after an apparent clinical cure, for instance through mercury, foci are still in existence which possess all of the histologic characteristics of the syphilitic infiltrate. Ehrmann has also demonstrated the remains of these infiltrates six months after the infection and three months after the outward manifestations had disappeared. He has therefore concluded that the exciting cause of syphilis in one form or another may remain in the lymphatic spaces and vessels in their vicinity, though the traces of its presence in the interior of the lymphatic vessels may have disappeared entirely.

It is a well-known fact that some time after the infection, not alone the sclerosis but the palpable lymphatic induration as well, may reappear in the same manner and form as that of the original infection, but without a new lymphadenitis. It is also known that when numerous scleroses were present all of them may reappear exactly in their original form. These facts teach us that the remaining residue or forms may again either multiply or become active and bring forth tissue-changes *in situ*, exactly similar to those which occurred at the time of the infection. In my service, Katzenstein found spirochetes on the site of healed syphilitic efflorescences on the genitals, Guszmann found them upon the tonsils and Pasini on still other organs, after the lapse of many years without any clinical symptoms having been observed.

The virulence of these spirochetes was also demonstrated by inoculation (Hoffmann). Recurrence is thus explained in the majority of cases

by these remaining spirochetal foci and it cannot therefore be assumed that any considerable number of spirochetes are constantly circulating in the blood-streams. For if this were so the outbreak in the later stages of syphilis would be of a generalized nature, while it is a fact that the number of syphilitic manifestations is diminished from one outbreak to another until the disease thus weakened in its infectious character is ultimately extinguished in the form of isolated gummata. In the same way the corymbose syphilide, consisting of numerous daughter foci in the immediate vicinity of a mother focus, distinctly indicates the proliferative capacity of the spirochetes, though they are in the main limited to certain localities.

It is probable that these latent foci do not bring about any clinical manifestations whatever. Probably the encapsulated spirochetes remain in a constant state of rest and multiply only when vascularization takes place, thus imparting specific substances to the blood and setting free tissue-reactions which give the clinical picture of recurrence. This is indicated by the fact as shown by Harold Boas, that the positive Wassermann reaction, disappearing after mercury has been administered, reappears long before the recurrence, thus acting as its precursor, or sometimes as its only symptom. From the present biologic point of view, and according to the investigations made by von Pirquet in regard to allergie, the syphilitic tissue-changes (roseola, papules) should be considered an effect of a local process of immunity, in the sense of a fixation of antigens and anti-bodies, in the same manner as it occurs in von Pirquet's tuberculin inoculation. We can therefore understand why some foci resist the influence of the remedy, only to succumb to reinjection later, when it is administered at the right time. This has already been sufficiently demonstrated by experience and may also be indicated by the following data: It is known that mercury exercises a direct destructive effect on spirochetes; and we may take it for granted that in many respects it acts upon them in a similar manner but not so effectively as salvarsan. Accordingly in the majority of cases a far greater number of spirochetal foci remain unaffected by the mercury treatment. Salvarsan undoubtedly displays a far greater spirillicidal power and consequently destroys all spirochetes wherever the slightest trace of the serum conveying it may be able to penetrate. As the result of many observations, not yet published, I have been enabled to determine the smallest amount of such a serum needed for an effective result. According to these studies, certain human sera to the amount of 0.04 c.c. are capable of curing almost unexceptionably, mice carrying in their blood innumerable trypanosomes, while other human or animal sera do not possess this power.

It is hard to believe how minute the amount of this trypanocidal substance contained in the serum may be. In the same way even slight traces of salvarsan probably act in the sense of a very powerful specific on the protoplasm of the spirochetes wherever it may reach them, even through osmosis. Various experiences support this view. In our earliest cases of syphilis doses of 0.25 gm. produced excellent effects on the symptoms. Likewise the absorption of a small part of the injected substance is usually sufficient to bring about a similar result. This is made evident by the fact that in cases in which necroses are rapidly formed, containing a large proportion of the salvarsan, the healing process advances quite satisfactorily. The following case will serve as an illustration:

CASE.—G. Presented two primary lesions about the size of a dime on the shaft of the penis. On September 7th, 0.5 gm. salvarsan was administered. On September 9th, the primary lesions were disappearing and on September 12th, epidermization was complete. On September 24th, an infiltration appeared at the site of injection which became distinctly necrotic five days later and on October 3d it was demarked and completely removed.

In this necrosis Professor Loeb found 0.0791 gm. arsenic which corresponds to 0.261 gm. salvarsan approximately. Thus the curative effect was highly satisfactory, though the absorption corresponded to less than one-half the injected dose. On the other hand it is seen that the small quantities of arsenic circulating in the blood display a clinically therapeutic effect even after several weeks. The following case appears to be particularly worthy of mention:

CASE.—Mrs. H. had some ten nodular, red efflorescences on the left nostril. On July 1st, a subcutaneous injection of 0.45 gm. neutral suspension was administered in the gluteal region. Most of the efflorescences healed rapidly, but on July 19th and August 26th, two nodules were still present. These created the suspicion that they might be of a lupous nature (syphilis and lupus combined) as they were exceedingly soft. We thought it was best to wait a while and verify the histologic nature of the nodules by inoculation. However on October 11th, the patient was perfectly well. There was not even a scar where the nodules had been situated. July 19th, Wassermann reaction, + + +. August 26th, + + +; October 11th −, that is, at the time of the clinical healing.

Still more remarkable is the effect of the small quantities of salvarsan which continue in circulation for a long time, as illustrated in the following case:

CASE.—M. Papular syphilide. Wassermann reaction, + + + +. On July 15th, he received 0.5 gm. salvarsan. August 27th, he reported as being cured; Wassermann reaction negative. At the site of injection a non-inflammatory infiltration was visible. September 15th, he showed a slight recurrence on the leg and the Wassermann reaction was + +. Without further treatment the symptoms of recurrence had almost disappeared on October 10th and the Wassermann reaction had again become negative.

Specific Anti-bodies.—With similar observations the question arises whether the enhanced effect of salvarsan as compared with mercury is solely responsible for the spirillicidal effect of the preparation. It is possible that we are dealing with a much more complicated biologic process; that is to say, the destruction of the spirochetes is followed by the liberation of endotoxines, the absorption of which causes the development of genuine anti-bodies. The question would naturally present itself whether or not the chemo-therapeutic effect of the remedy is associated with an anti-body formation. Analogies are offered in this respect by the effect of other preparations of arsenic in trypanosomiasis, especially of arsenophenylglycin. In this disease it has been observed that they exert a far more favourable influence in rabbits that have been infected with trypanosomes, than in mice, guinea-pigs, or horses. Ehrlich and his co-workers have demonstrated the reason for this phenomenon. They have shown that the rabbit's organism being better suited to the production of anti-bodies than that of the other animals mentioned, anti-bodies appear immediately under the influence of the dead trypanosomes. This fact has also been demonstrated most convincingly by Schilling. In the rabbit, arsenophenylglycin destroys only the major portion of the trypanosomes. These chemo-therapeutic processes bring about the development of anti-bodies, which in turn cause the death of the remaining trypanosomes. We can thus see that the actual sterilization is accomplished as the result of a combined chemo- and serotherapeutic process.

In the other animals such a formation of anti-bodies does not occur, or if it does occur it is incomplete and therefore a fractional number of the parasites will remain. Consequently in cases in which curative effects take place without the introduction of additional salvarsan after a long period or even after a brief interval, we must necessarily attribute these lingering cures to the effect of small doses of arsenic still circulating in the blood, combined with newly formed anti-bodies. It is a well established fact that the ulcerous and malignant types particularly in the tertiary stage, are influenced most favourably by the remedy. This is probably due to the

fact demonstrated by Finger and Landsteiner, that in this stage of the disease the organism reacts according to the general law of allergie, that is to say, it is especially disposed towards the production of anti-bodies.

Ehrlich also assumes that this is the case, as a result of the observations made by Taege, Duhot, Dobrowitsch and Raubischek. These observers treated hereditary syphilis in children through the milk of the mothers who had been injected with salvarsan, and Scholtz found that such milk contains no arsenic or only slight traces of the drug.

Taege: "Erfolgreiche Behandlung eines syphilitischen Säuglings durch Behandlung seiner stillenden Mutter mit 606" (*Münchener medizinische Wochenschrift*, 1910, No. 33):

CASE.—Rosa H., aged nineteen, single, in the last month of pregnancy; was admitted to the clinic for skin diseases on the day before delivery. Date of infection unknown. In May 1910, the first eruption appeared on the skin. Patient is of strong build, weight 140 pounds, kidneys and eyes normal. Leucoderma of the neck, extraordinarily large and broad condylomata on the genitals; numerous spirochetes present. Wassermann reaction strongly positive. We were tempted to treat the girl at once with salvarsan and thus exert a simultaneous influence on the mother and her child. This would have been analogous to the method hitherto employed of treating pregnant women with inunctions of mercury. On the one hand however, there was the objection that it was impossible to determine the exact date of delivery. It might take place in a day or in a week, and consequently the remedy would have but a day or a week within which to produce the desired effect. As a result the anticipated symptoms in the child might be influenced by the remedy, if fully developed they might be completely obliterated, or possibly they might not have existed at all.

On the other hand, the vigourous fœtal uterine movements warranted the expectation that the child would enjoy vitality after birth, and as the maternal breasts were well developed it was hoped that she would be fully able to nurse her child.

Consequently Professor Jacobi determined that he would not administer an injection of salvarsan until after delivery, so that we might observe the effect of the treatment of the nursing mother upon the infant.

Delivery took place at the Woman's Clinic on July 4th. Both mother and child were transferred to the Children's Clinic on July 9th, and on July 12th the mother returned to the Clinic for skin diseases with her son, who was now one week old. There was no change in the mother's symptoms.

When the child was born it weighed nearly five pounds. It was carried to full term, but was colourless, wilted and senile. It did not cry, but lay apathetically and refused to take the breast. At the root of the nose a slight depression could be seen. On the twelfth, no specific symptoms were visible. On the thirteenth,

however, the appearance of four pemphigus vesicles on the sole of the left foot and one on that of the right was noted. They had become much larger on the fourteenth. There was also a syphilitic paronychia on three fingers of the right hand and on one of the left. This tendency of the disease to extend having been established beyond a doubt, I decided to hesitate no longer. On the evening of July 14th, I therefore administered an injection of 0.3 gm. salvarsan, in pure aqueous solution, into both buttocks of the mother. On the third day, local pain appeared. On the fourth day, a lentil-like red exanthem appeared on the trunk; headache on the fifth day. After the third day, there was a striking recession of the moist, foul-smelling condylomata; spirochetes absent. On the tenth day the Wassermann reaction was still positive.

In all other respects, the usual picture of the effects of salvarsan was present. As to the child: The existing symptoms became more marked on the first and second days after the mother's treatment. After the third day, there was no further progress and then a sudden recession of all the symptoms took place. On the fifth day after the injection (July 19th), we noted: The grey fawn colour has changed to a normal red; paronychia absent; pemphigus gone, except a small spot on which marginal scales of the dried vesicle are still visible. The child does not wail, but cries out vigourously; he empties the breast at each feeding.

Hence we have attained a noteworthy improvement! When discharged on July 29th, the child weighed eight pounds and did not exhibit any symptoms of syphilis. Of course, it is difficult to prove how the cure had been effected. At first I thought that some of the salvarsan had been transferred to the infant with the milk, or if not that, perhaps some arsenious acid which might have been liberated. Both of these conclusions were erroneous. With Marsh's test, I was unable to determine even a trace of organic arsenic in 100 gms. of milk collected; and I found but a trace of inorganic arsenic when the milk was treated with HCl and $KClO_3$.

Ehrlich stated to Professor Jacobi orally, that according to his opinion, which he has demonstrated to be a fact, a large quantity of endotoxines is liberated by a sudden destruction of the spirochetes. This brings about the formation of antitoxines, and it is supposed that the latter enter the milk.

Duhot: "Unerwartete Resultate bei einem hereditär-syphilitischen Säugling nach Behandlung der Mutter mit 606" (*Münchener medizinische Wochenschrift*, 1910, No. 35):

D. M., aged twenty-two. Infected through marriage by her husband. Was admitted to the clinic with a generalized roseola in March 1908. Being exceedingly debilitated, the patient did not tolerate the injections of grey oil very well. She was then systematically treated, receiving thirty inunctions, each of 7 gm.

grey ointment and iodide of potassium internally. Her weight had constantly decreased and in December 1909, her weight while pregnant had been reduced to ninety-nine pounds. The tuberculin reaction did not indicate the presence of tuberculosis. In November 1909, malignant tuberculo-ulcerous syphilides appeared in both parotid regions. They had an unctuous substratum and violet-coloured, elevated borders, and after months of specific treatment and energetic local cauterization with the nitrate of silver stick, these ulcers disappeared very slowly. The scars which remained after the ulcers had healed became converted into coarse keloids which disfigured the patient considerably. These ulcerations had barely healed when new ulcerations appeared which extended to the cheeks and forehead. These ulcers had likewise not yet been healed when, in spite of continued treatment, three new ulcerating surfaces, deep and extensive, made their appearance. They covered the forehead and the root of the nose and also the entire supraorbital region and upper portion of the cheek of the left side. The borders of the ulcers are in part sharply outlined and partly elevated, and although the patient's general condition has improved somewhat her appearance is actually repulsive. In the course of a year and a half the ulcers had completely destroyed the patient's face, in spite of our most vigourous efforts in her behalf.

On July 4th, a fully developed female child was born, weighing less than six pounds. *Status præsens:* The child's skin is red and wrinkled and it possesses the characteristic aged appearance of children with hereditary syphilis. The child's cry is very faint and it nurses very sparsely; it is also afflicted with a nasal catarrh. Several days after birth, papular efflorescences appeared on the body and trunk, and red papules and small isolated pemphigus vesicles on the soles of the feet. The child does not convey the impression of having any vitality. From July 4th to the 25th, its weight increased only three ounces.

As the ulcers in the mother's face continued to spread, we administered an injection of 0.5 gm. salvarsan into the right gluteal region on July 25th and on the following day, 0.45 gm. was injected into the left gluteal region.[1] Although the pain was severe it was tolerated without an anesthetic. As early as the following day, the substratum of the ulcers had changed to such an extent that they were no longer recognizable. On August 6, 1910, twelve days after the injection, the deep ulceration was cicatrized. All of those who had the opportunity of following the course taken by this curative process agree with us that the rapidity with which it progressed was actually wonderful. But we were still more surprised when we observed the changes that occurred in the child on the third day. The dark red colour of its skin had assumed a rosy hue, the efflorescences and vesicles had disappeared, as had the nasal catarrh, and the child nursed very well. We therefore assumed that these sudden changes were to be attributed to

[1] 1.0 gm. is the dose we usually administer to adults with good constitution without causing any organic injury.

the injection of salvarsan and we watched the future developments very carefully. The milk was analyzed at once, but our assistant, Dr. Van Keerberghe, was unable to detect the presence of even a trace of arsenic. The result of his examinations was negative.

During the first week the child gained sixteen ounces in weight, fifteen ounces in the second week, and nine ounces in the third. It is thus seen that although the infant gained but three ounces from July 4th to July 25th, it gained about forty ounces during the three weeks from July 25th to August 18th. The general condition of the child also changed completely. The skin covered the muscles snugly and the latter assumed a firmer consistency. The senile appearance was entirely replaced by an altogether normal expression. A slight degree of hydrocephalus still exists.

Furthermore Dr. Mathias Dobrowitsch, of Pzsony, confirms the favourable influence of the remedy on the nursing child through the mother who had been treated with the remedy (Über Heilwirkung von Ehrlichs 606 durch die Mutter auf den Säugling, *Wiener klinische Wochenschrift*, 1910, No. 38).

Mrs. A. C., aged twenty-four. Denies syphilitic history. During the four years since her marriage she has had two abortions; her youngest child is now four months old. Soon after its birth this child had a vesicular eruption which received no medical treatment as it was considered harmless. However, this eruption has continued to extend until to-day (August 20th) it covers the thighs, face, back and arms in the form of a copper-coloured, scaly eruption. In various portions of the body crops of vesicles may be seen; in addition there is a secreting ulcer at the flexure of the groin and the knee-joint, while the palms of the hands and the soles of the feet glisten like parchment and desquamate easily. Bleeding rhagades are visible between the toes, in the mouth, nose, eyes and anus. Breathing through the nose filled with secretion is very difficult. There are no clinical manifestations in the mother. Wassermann reaction, + +. The mother has been nursing the child, which has been losing flesh for some time past. The father has avoided an examination. On August 23d, an injection of 0.6 gm. salvarsan was administered under the dorsal skin of the mother. Rising temperature and considerable pain as well as extensive swelling at the site of injection followed for four days, the temperature being 101° F. on August 23d, 102° F. on the 24th, 99° F. on the 25th, and 101° F. on the 26th. The pain and temperature receded on August 27th, and the patient felt perfectly well. On August 27th, the *status præsens* of the child was as follows: The rhagades on the various orifices of the body are healed; the scaly eruptions have become smooth, of a pale brown colour and a bran-like desquamation; the secreting ulcers in the flexure of the groin and the knee-joint have grown a new epithelium; the soles of

granted that cases of recurrence, particularly when of severe character, will return for observation in greater numbers in the event of a new method of treatment being employed than the cases which were completely cured. Sieskind's tabulations, covering 375 cases treated, show the following: Of 232 men treated, thirty-five returned to the clinics, and among them there were seven cases of recurrence. Of 134 women treated, nine returned for observation and of this number there was one recurrence. The subjoined table which also contains the cases in which an exanthem appeared in primary cases after treatment with salvarsan, will give full details.

I have seen moderately severe recurrences only four times,—one case of impetigo capitis, one case with fifteen groups of a papular and somewhat crust-covered exanthem, once a papular syphilide on the palms of the hands and extremities, and one eruption with twenty areas on the forearm resembling psoriasis. But in most cases there were recurrences of circumscribed areas, patches on the tonsils, iritis, choroiditis, once trochlearis, once abducent paralysis and one case of auditory nerve disturbance. The general impression conveyed is that an epoch in the progress of syphilis, as manifested by the mercurial therapy, had been passed over. This would also be made evident by the proportionately frequent appearance of foci in the nervous system. The relapses unquestionably partake of the character of a late recurrence. But their greatest importance consists rather in their localization and not in their obstinacy, because they soon disappeared when another injection had been administered, whereas some of them seemed to resist the administration of mercury. This also proved that the spirochetes had not become salvarsan-fast, a condition which, according to the explanation given above could not have been taken for granted, as the encapsulated centres do not come into contact with the remedy at all. In general a conclusive judgment on the questions of recurrence and permanency of the cure cannot yet be announced, and for this reason, the value of the respective methods of treatment as they refer to these questions, cannot as yet be positively stated.

Therapy.—If our viewpoint should prove to be correct, a second injection of the new remedy ought to be administered in most of the recurring cases, as it invariably destroys far more of the circumscribed foci of spirochetes than mercury is capable of doing.

From these statements we find a new point of view for a rational therapy. Wherever symptoms of syphilis are present, it appears to be absolutely necessary to employ the most effective known remedy. On the other hand there is no reason whatever for administering the remedy

Data of Recurring Cases

Number	Name of Patient	Diagnosis	Before Injection: Spirochetes	Before Injection: Wassermann Reaction	First Injection Date Dose	After Injection: Spirochetes	After Injection: Wassermann Reaction	Result	Recurrence During Stay in Hospital	Second Injection Date Dose	Date of Discharge	Condition at Time of Discharge	Recurrence After Discharge	Second Injection After Readmission	Date of Second Discharge	Condition at Time of Second Discharge	Date of Return for Observation	Remarks
1.	P.	Malignant lues.	−	++++	21 V. 0.40 gm.	−	++++	Cured.	21/VII. Left tibial periostitis.	26/VII. 0.50 gm.	6/VIII.	Improved.	.....	.....	.....	.....	25/VIII.	Cured.
2.	Gr.	Gangrenous chancre.	+	++++	5 VII. 0.52 gm.	−	++++	Chancre healed.	17 VIII. Roseola.	20/VIII. 0.50 gm.	6 IX.	Cured.	.....	.....	.....	.....	.....	Outbreak of secondary symptoms after disappearance of chancre.
3.	K.	Chancre.	+	++++	20 VII. 0.50 gm.		−	Chancre healed.	.....	.....	10 VIII.	Cured.	12 VIII. Papular exanthem.	20 VIII. 0.50 gm.	5 IX.	Papular exanthem gone.	.....	Outbreak of secondary symptoms after disappearance of chancre.
4.	M.	Papular syphilide about anus, etc.		++++	22 V. 0.30 gm.		27 V. ++++ 14 VI. ++	.....	.....	.....	29 VI.	Improved. Syphilide still present.	Circinate roseola. Papular iritis.	.....	.....	.....	26 VIII.	
5.	W.	Roseola. Angina. Plaques.		++++	26 VI. 0.50 gm.		3 VII. + 13 VII.	Cured.	.....	.....	16 VII.	Cured.	Iritis, erosion of primary scar.	.....	.....	.....	6 VIII.	
6.	F.	Chancre.	+	+	18 VIII. 0.52 gm.	−	−	Chancre epidermized.	Eroded papule on scrotum.	.....	.....	.....	.....	.....	.....	.....	.....	Outbreak of secondary symptoms after disappearance of chancre.
7.	Gü.	Patches of tonsils and lips.		++++	5 VII. 0.52 gm.		++++	Cured.	.....	.....	.....	.....	Specific iritis.	.....	.....	.....	9/IX.	
8.	Mrs. F.	Ulcerocrustaceous syphilide.		+	13/VI. 0.47 gm.		17 VI. + 21/VI. −	Cured.	.....	.....	24/VI.	.....	The same syphilide in lighter form.	.....	.....	.....	1/IX.	

intermittently when there are no such symptoms, inasmuch as with a thorough clinical and serological control an approaching danger to the patient can be recognized and combated in due time. Again after an injection of salvarsan there is a probability of attaining a *sterilisatio magna* in at least a part of the cases. The fact that the positive Wassermann reaction remains or returns, seems to indicate that according to our present knowledge, a latent focus of spirochetes is present which communicates with the circulation. The dangers of such a focus consist not so much in the possibility that a new invasion of spirochetes might proceed from it, but that it might increase in size locally and cause disturbances which may be of greater or less importance, this depending on the value of the organ or part of the organ attacked (heart or brain).

It is certainly a goal in therapy well worth striving for, namely that a syphilitic shall be made permanently free of all symptoms and also of the Wassermann reaction. However, not unlike other symptoms of syphilis, the positive Wassermann reaction also remains refractory to mercurial therapy, and Kraus is probably correct when he asserts that such cases, as far as ultimate prognosis is concerned (*quoad sanationem*) should be considered as being unfavourable. He even holds the fear to be justified, that paralytics are recruited entirely from those cases which continually remain positive, in view of the fact that all paralytics whether previously treated or not react positively to the Wassermann reaction. From our experience with the new remedy when administered to cases that have resisted mercury, it is to be hoped that a large part of these positive Wassermann reactions which are refractory to mercury may be eradicated through salvarsan. For this reason we have administered the treatment in such cases, but as to the success thus far attained we cannot as yet render any report, inasmuch as the period of observation has not been of sufficient duration. However, since according to Alt, whose observations extend over a prolonged period, the Wassermann reaction may be made permanently negative by the new method of treatment even in paralytics, it may be assumed that this result might be attained still more readily in more recent cases of syphilis. Still it is true that we do not yet possess a safe criterion for determining when syphilis is absolutely cured. Absolute scientific proof cannot be adduced in a disease which after decades of latency may without warning, bring forth infectious secondary symptoms, as demonstrated by Fournier in his excellent book on secondary tardy syphilis.

Speaking generally however, when a syphilitic does not exhibit any

symptoms for a period of two years and with control tests made every three or four months shows a repeatedly negative Wassermann reaction, the disease may be considered cured. Hitherto conservative authorities have considered four years with an absence of symptoms and without treatment, necessary for consent to marry. With the remarkable refinement of diagnosis obtained through the Wassermann reaction, which makes evident the minutest syphilitic focus in the body, half of the period of complete freedom from symptoms is a far better standard by which to estimate the risk of infection. Even taking into consideration the fact that some syphilitics give a negative Wassermann reaction, it is not safe to say that a permanent negative reaction has been attained in these cases. The following observation shows how careful we must be in this respect; on the other hand it also represents the longest period of observation in a syphilitic in whom a number of investigations revealed a constantly negative Wassermann reaction.[1]

A young colleague who infected himself on August 1, 1908, observed a minute erosion on the shaft of the penis, near the symphysis, on August 15th. This I diagnosed as a primary affection, spirochetes +, on August 28th. Inguinal scleradenitis present. Serodiagnosis negative. 140 gm. grey ointment. On November 30th, he presented slight patches on the tonsils; no other symptoms; received 120 gm. grey ointment. Serodiagnosis negative. Since then there have been no symptoms whatever and his general condition is excellent. However, on September 15, 1909, the Wassermann reaction was + for the first time.

Consequently it is also necessary to consider the Wassermann reaction as a symptom of syphilis which requires treatment. However, taking into consideration the fact that the Wassermann reaction can become negative only six or seven weeks after the injection and that an unlimited growth of the spirochetes need not be feared, it is not necessary to repeat the injections at too brief an interval simply because the Wassermann reaction made its appearance. Three months may be selected as a proper interval between these reinjections. We should wait a sufficiently long time to determine whether or not permanently resistant cases will be found in this way. It is obvious that we may also avail ourselves of our other means of treatment, mercury and iodides, in cases in which salvarsan has failed to produce a wholly favourable result. According to the present state of our knowledge we may safely recommend that the first treatment should consist of an

[1] **Wechselmann**: "Die therapeutische Bedeutung der Wassermannschen Reaktion in Wolff-Eisner's Handbuch der Serumtherapie."

injection of salvarsan. In cases with papular syphilides, in order to create conditions more favourable to the attack, we generally employ mercury for two weeks because mercury promotes the absorption of the infiltration and thus makes the vessels more easily penetrable. Then we inject the salvarsan.

It should be remembered that we are only at the beginning of our knowledge of the new treatment and that this knowledge exhibits many gaps. However, with the growth of our experience the confidence in the new method of treatment has been constantly increasing, together with the hope that we shall thus learn to cure syphilis, or at least to greatly limit its ravages. Most of its terrors have already vanished since malignant syphilis has been successfully cured.

But we also entertain the hope that the new method, in association with the refinement of diagnosis made possible by the Wassermann reaction may afford a means of preventing the development of paralysis and tabes. If even but a part of these hopes are realized, and only an extreme degree of pessimism can doubt it, Ehrlich has undoubtedly scored an achievement of the highest scientific character and also one of the most magnificent victories of civilization.

ADDENDUM

After the conclusion of this work, upon the advice of Ehrlich, we began the employment of the intravenous method, and in the past three weeks we have given more than one hundred of these injections. The method is easily carried out, and as far as the patient is concerned, it is by far the most agreeable. But in its effect on the symptoms of syphilis it does not seem to have any advantage over the other methods of administration, especially the subcutaneous injection of the neutral emulsion. In papular syphilides we have frequently repeated the injection after fourteen days with satisfactory result. Whether however, this method enjoys the same—we might add, complete—freedom from danger that is exhibited by the subcutaneous method remains to be seen. Until then however, the latter method must be given the preference in doubtful cases in which the circulatory organs or the central nervous system are involved.

The objections brought forth against this method on the ground of the occurrence of necrosis are widely exaggerated. Only in the month of August did we see this complication to any noteworthy extent. In the total of 1,500 injections we observed necrosis not very often, and particularly in the last 100 cases; with the more exact attention to the technique, which has already been described, we encountered infiltrations of a moderate degree, but not a single case of skin necrosis. Very often, as a matter of fact, in cases [illegible] after our injection and also in a few cases [illegible] the site of the injection could not be determined.

[illegible]

of by filtering the solution through sterile gauze. The solution should be absolutely clear and free of particles. We now add 0.7 c.c. normal sodium hydrate (four per cent. by volume) for each 0.1 gm. of salvarsan used; the turbidity which results passes off by continuous shaking of the cylinder. To this is added sterile salt solution—50 c.c. for each 0.1 gm. of the substance. It is generally believed that the acid solution is very dangerous, even deadly; nevertheless we once administered, by mistake, an acid solution, 0.4 : 200, without the slightest injury. The technique is greatly facilitated by inserting a glass tube, armed on its end with a piece of rubber tubing, between the syringe and the Schreiber cock. In this way displacement of the needle in the vein is prevented while drawing the fluid into the syringe or through the movement of the syringe. Fixation of the needle is also made easier. The venous blood is visible through the glass tube. This is not reinjected into the vein but is permitted to flow out through the outgoing cock, to which a glass tube with rubber connection is attached. Then the fluid is injected. We use a 10 c.c. Record syringe, because the 20 c.c. syringes are removed with some difficulty from the narrow needle. The Luer glass syringe is not practicable, owing to the fine attachment for the cock, which is easily broken.

As far as possible we select one of the smaller veins of the forearm because the needle rests more firmly than in a larger vessel. By giving the vein a short, sharp blow with a sterile towel the walls of the vessel contract and resemble a cord or string; this makes the entry of the needle much easier. The needle is made to follow the upper wall of the vein as nearly as possible. We draw some blood into the syringe which is about three-quarters full of the salt solution and we now know that the needle is properly fixed in the vein. This blood is permitted to flow out into a vessel, the tube is loosened, and we inject the salvarsan solution. With the smaller syringe this can be accomplished in a very short time—two minutes.

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APPENDIX

The Technique and Methods of Injection of Salvarsan

BY

ABR. L. WOLBARST. M.D.

Coincident with the appearance of the first edition of this translation of Wechselmann's work, in February 1911, salvarsan became accessible to the general medical profession. Until that time its use was confined to a limited number of clinicians, to whom Professor Ehrlich had entrusted some forty thousand sample ampuls, which were to be tested in actual practice. It was immediately seized upon everywhere, in the hope and in many quarters in the belief, that at last the long-looked-for specific for syphilis was at hand.

It was to be expected that a remedy which was created synthetically, as was salvarsan, to meet and overcome certain diseased conditions, would excite unusual anticipations, and by the same token, keen disappointments. At this writing (October 1911), at least one hundred thousand injections, and possibly a great many more, have been administered, and though the first shock of its brilliant results has passed off, we may safely say that the remedy stands to-day incomparably superior to anything that has yet been produced for the conquest of syphilis.

Even those who are not overenthusiastic as to its merits concede that salvarsan does exert a powerful, though ephemeral influence on syphilis and its lesions. These writers (principally Marshall, of London), while admitting that salvarsan gives brilliant results at times, maintain that they have seen equally brilliant results with the use of mercury and iodides, without at the same time subjecting the patient to the alleged risks and dangers that go with salvarsan. It does seem strange that so small a number of observers should have obtained results directly contradictory to those obtained by the preponderating majority of clinicians throughout the world, and we cannot

but feel that the persistent failures encountered by these observers have not been due so much to the failure of salvarsan itself, as to its employment in unsuitable cases associated with some cardinal fault in the technique.

There is still much to be learned regarding salvarsan. We are not yet sure of the proper dose, nor of the number of times in which it should be given. We do not yet know its exact effects on the nervous system, nor do we know what ultimate after-effects may follow its administration in the general economy. And lastly, we are not yet sure of the best method of introducing salvarsan into the body. All of these data will be determined with the flight of time; in view of these conditions, therefore, a general résumé of what we have learned in one year's experience with salvarsan may not be considered out of place.

Dosage.—The general consensus of opinon is that 0.6 gm. is the most effective quantity, consistent with safety, when administered intramuscularly; for the intravenous injection, there seems to be a tendency to set the most useful dose at 0.4 gm. for males, and 0.3 gm. for females. Speaking for myself, I have given 0.6 gm. in both sexes intravenously without any serious, untoward results. It goes without saying that extreme caution should be exercised in feeble patients, or in patients who have severe lesions of the circulatory and nervous system. In such cases, excellent results may be obtained by giving a small dose and repeating it at intervals of several days.

Duhot (*Annales de la Policlinique Centrale de Bruxelles*, Nos. 5–7, 1910) gives much larger doses than those just mentioned. He believes that salvarsan is non-toxic and he administers it in this dosage:

To robust men, 0.7 to 1.0 gm.; to feeble men, 0.5 to 0.7 gm.;

To robust women, 0.5 to 1.0 gm.; to feeble women 0.4 to 0.6 gm. He has given salvarsan in 225 cases without failure or recurrence.

Contraindications.—Wechselmann's list of contraindications (page 69) stands unaltered in the light of our greater experience of to-day. It may be said that salvarsan is a safe drug to use, but its greatest field for harm is to be found in those persons that possess an idiosyncrasy to arsenic. When the list of fatalities following the use of salvarsan is carefully studied, it will be observed that death has not been the result of arsenic toxemia, but rather the result of a hypersensitiveness towards the drug that could not have been foretold in advance, except by the administration of small doses of arsenic before the injection. Briefly we might say that cardiac and extensive nerve lesions constitute the only contraindications that exist against the use of salvarsan, and even in these conditions, the remedy may

be used in the majority of cases, if due precautions are employed against too large a dose.

Wechselmann has recently stated (*Münchener medizinische Wochenschrift*, No. 28, 1911), that he has thus far given 4,500 injections, of which 2,500 were given subcutaneously and 2,000 intravenously. In all of these cases he has not encountered a single instance of arsenic intoxication. Other writers have shown that whenever unfavourable sequelæ have developed, they have manifested themselves principally in the nervous system. Konrad Alt, who has had extensive experience with salvarsan, has stated (Bresler: *Psychiatrisch-Neurologische Wochenschrift*, No. 5, 1911) that seventy-five per cent. of deaths following the use of salvarsan have been in cases of pre-existing severe disease of the nervous system. The number of spirochetes being small in these cases, Ehrlich has advised that a smaller dose, i.e., 0.4 gm., is sufficient to destroy them. He declares that salvarsan kills all spirochetes that are within reach, and also those in new growths and tissues. The breaking up of these structures sets up a reaction process. In the brain or spinal cord, such a change in the local and general pressure might easily bring about symptoms of paralysis or irritant phenomena, which, as a rule, are but ephemeral. In all cases with a tendency towards excitement and convulsions, the remedy should not be used; likewise in old cases of paralysis, or where the paralysis has become spastic in type. In the early stages of tabes and general paralysis a great many cases have shown subjective and objective improvement, but there is no record of a complete cure in tabes or paresis.

On the other hand, Mattauschek believes that salvarsan is an unusually energetic and effective therapeutic agent in diseases of the nervous system, caused by syphilis; if it is used with perfect technique, it is almost without danger. In all cases demanding a prompt result, it should be used (*Zeitschrift für die gesammte Neurologie und Psychiatrie*, April 11, 1911).

Clinical Recurrence.—Clinical recurrence has followed the treatment with salvarsan, in a percentage of cases, that varies from ten to fifty per cent., according to the respective observer. My own experience, based on fifty cases studied for a period averaging about six months, indicates that clinical recurrence follows one intramuscular injection in about twenty per cent. of the cases (*New York Medical Journal*, September 16–23, 1911). The period that elapsed between the injection and the appearance of the clinical recurrence, varied from one month to eight months. For several months past I have used the intravenous method, repeated once or twice, and the average of recurrence has been reduced considerably.

In 126 cases of neuro-recurrence out of a total of 14,000 injections, Bennario (*Münchener medizinische Wochenschrift*, April 4, 1911) found that the nerves principally affected were the optic, oculomotor, trochlear, trigeminus, abducens, facial and auditory. He thinks, with numerous other observers, that these phenomena are not of a toxic nature, but rather the clinical manifestations of a swelling induced by the preexisting pathologic process. A number of writers urge that the ears should be examined before an injection of salvarsan is given, in view of the large number of auditory nerve recidiv (neuro recurrence).

Recurrence after injection with salvarsan may be explained in this way: Certain tissues which harbour the spirochetes when situated in a mass of dense fibrous connective tissue, are poorly supplied with blood and lymph. These tissues cannot be reached by the injected fluid, and they may become active again under favourable conditions, and relapse, like other pathologic conditions, notably tuberculosis. These relapses are best treated by repeated injections of salvarsan.

Elimination.—Early in our experience with salvarsan, it was believed that salvarsan is totally eliminated in the urine within a week to ten days after the injection. Recent studies by Heuser (*Medizinische klinik*, April 9, 1911), however, have shown that in some cases arsenic can be found in the urine six to nine months after an intramuscular injection, and as long as three months after an intravenous injection. In one of his cases, arsenic was found not only in the urine, but in the blood as well. These observations have been confirmed by Frenkel-Heiden and Navassart (*Berliner klinische Wochenschrift*, July 24, 1911).

Bornstein (*Deutsche medizinische Wochenschrift*, January 19, 1911) found that salvarsan given intravenously does not remain free in the blood, but is deposited in the liver, spleen and kidneys. He found 0.0031 gm. in the form of trioxide in the kidneys and over twice this amount in the liver of a man who died two weeks after receiving an injection of salvarsan.

A case of acute degeneration of the kidney, similar to acute poisoning by corrosive sublimate, after an injection of salvarsan, is reported by Weiler and Mohr (*Medizinische Klinik*, April 15, 1911). The disturbance in the kidneys rapidly subsided with the elimination of the arsenic. This kidney irritation seems to be more severe when salvarsan is given intramuscularly. These writers believe that salvarsan undergoes a toxic transformation in the muscular deposits. I have personally reported a case of suppression of urine with marked scarlatinal rash and a temperature of 105.4° F. which also passed off simultaneously with the increased elimination of the arsenic,

induced by the administration of diuretics and saline purges (*Interstate Medical Journal*, January 1911). On the other hand, it is a common observation that chronic nephritis on a syphilitic base, readily responds to salvarsan.

Salvarsanized Milk.—The promising results of Taege, Duhot, Dobrowitsch and Raubischek, in treating syphilitic infants by injecting the nursing mother, have not been repeated in the experience of later observers. Jesionek treated a number of infants with the milk of syphilitic mothers who had been injected with salvarsan intravenously. There was some improvement, but not as great as was expected (*Münchener medizinische Wochenschrift*, May 30, 1911).

Analysis showed that there were appreciable amounts of arsenic in the milk, and probably endotoxins and antibodies. He recommends feeding such infants with milk of goats or cows that have received a dose of salvarsan, since in this way no further endotoxins would be introduced into the infant's system. In one case in which the experiment was tried, the curative effect was much greater than with the administration of mother's milk. There is no doubt that the addition of more endotoxin to the quantity already in the body of the infant is a real danger that should be avoided.

Technique and Methods of Employment

Various methods have been devised for the administration of salvarsan, and most of them have some special advantage that commends it to its advocate. All of these methods have been tried, but it may be said to be the consensus of opinion that they stand in this order, in respect of their effectiveness and general utility: 1. Intravenous; 2. Intramuscular injection of an alkaline solution (method of Alt); 3. Oily emulsion; 4. Acid solution; 5. Neutral emulsion.

Chemically salvarsan may appear in various forms by varying the method of solution, thus:

A biacid solution is formed when salvarsan is dissolved in water;

A monacid solution is formed when it is dissolved in water with one molecular proportion of sodium hydroxide;

A neutral suspension is formed when it is dissolved in water with two molecular proportions of sodium hydroxide;

An alkaline suspension is formed when it is dissolved in water with three molecular proportions of sodium hydroxide;

An alkaline solution is formed when it is dissolved in water with four molecular proportions of sodium hydroxide.

The Intravenous Method.—Wechselmann has described in detail his subcutaneous method of injection. Its obvious disadvantages and its tendency to the formation of necrosis and infiltration have led him to discard it in favour of the intravenous method, as first advocated by Iversen, Weintraud and Schreiber. The intramuscular method of Alt has also been largely discarded in favour of the intravenous method, principally because of its painfulness. While most patients suffer very little pain, some do suffer excruciating pain, which may be associated with actual neuritis and nerve degeneration after such an injection. The intravenous method is absolutely devoid of pain, and it is also without intrinsic danger, when properly given. Ehrlich himself has become quite enthusiastic over this method, because of the ease with which it may be given and repeated from time to time. He recommends that an intravenous injection should be repeated twice at intervals of two weeks, in order to obtain the maximum curative effect.

Neisser gives three intravenous injections within three to six weeks, at the same time giving a vigourous course of mercury (*Deutsche medizinische Wochenschrift*, No. 41, 1910). Marschalko and other observers also believe that the injections should be supplemented by mercury. Still others recom-

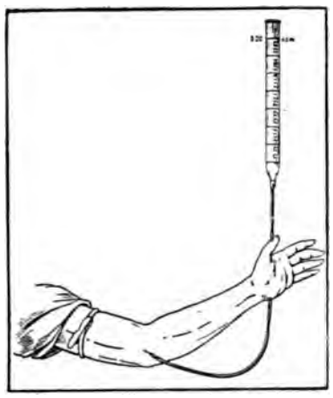


FIG. 1.—Weintraub, Intravenous Apparatus.

FIG. 2.—Schreiber, Intravenous Method.

mend that the intravenous injection be followed in a few days by an intramuscular injection (Iversen).

The exact technique of the injection, while differing in matters of detail, according to the style of apparatus employed, is essentially the same in all methods. The essential requirements are, 1st, a slightly alkaline solution of salvarsan; 2d, 300 c.c. of sterile physiologic salt solution; 3d,

an apparatus and needle for driving this solution into the selected vein. Thus, Weintraud depends on gravity for his driving force (Fig. 1), Schreiber uses a complicated system of syringe and cocks (Fig. 2), and Iversen uses a simple rubber bulb (Fig. 3), as a pump. I have seen all of these methods tested, but for simplicity, reliability and effectiveness, the Iversen apparatus seems to me to be superior to any other apparatus that has yet been devised. I have described this apparatus in detail, with some

FIG. 3.—Iversen-Wolbarst Intravenous Apparatus.

modifications (*Medical Record*, May 13, 1911) and have used it in several hundred cases with absolute satisfaction (Fig. 3). The technique that I employ is as follows:

All apparatus used must be absolutely sterile, and the surgeon should prepare as for a surgical operation. The regular operating-room should be used, and not the bedside.

The dose of salvarsan, 0.6 gm., for instance, is dissolved in ten or fifteen c.c. of sterile, hot distilled water, in a glass mortar. This solution should be absolutely clear and canary yellow in colour. To this is added sufficient

of a sterile fifteen per cent. solution of sodium hydrate, drop by drop, to convert the biacid solution into an alkaline solution. Usually it takes about twenty-three drops to prepare this alkaline solution. If the lye solution is not absolutely fresh it may require as many as forty or fifty drops. Hence it is well to have a fresh solution. The alkaline salvarsan solution is now poured into the flask of the apparatus, being filtered for safety sake, and 300 c.c. of sterile, physiologic saline solution (0.9 per cent.) added, this also being filtered through several thicknesses of sterile gauze. The saline should be of blood temperature, and should be made of absolutely fresh distilled water, double boiled, with chemically pure sodium chlorid, not ordinary salt. The solution is now ready for use. The neck of the jar is closed with its rubber stopper, and the rubber air-bulb is squeezed a few times so as to pump out whatever air there may be in the tubing or flask. The stop-cock in the glass window is now closed, and we are ready for the injection. Meantime an assistant has sterilized the skin of the arm, at the point where the injection is to be made. The patient lies on the operating-table with his arm resting at right angles to his body, on an extension. A rubber tourniquet or stout catheter is tied about the arm and held there with an artery clamp, until the selected vein stands out prominently. The needle is now tested as to the patency of its lumen, by inserting the thickest copper wire that it will accommodate, also sterile. The needle is now inserted under the skin, and gently yet firmly introduced into the swollen vein. Blood flows freely, and we are certain that the needle is properly situated within the vein, and not outside of it. The tourniquet is now released. The stopcock in the glass window of the apparatus is now opened, permitting the solution to escape through the end of the tube. This drives out any air remaining, and while the fluid is thus escaping, the canula is quickly fitted into the collar of the needle, and the fluid is now flowing easily and painlessly into the vein. There is enough air-pressure in the expanded air-bag to expel the entire contents of the jar into the vein without any further manipulation, but it is better to see that the air-bag is kept filled with air, thus insuring the continuity of the flow.

There are three guides by which we can tell whether or not the fluid is entering the vein properly: 1. The fluid in the jar is diminishing in quantity; this is noted by watching the graduations. 2. The glass window shows nothing but clear, canary-yellow fluid passing through; if there is any trouble with the flow, there is a backward flow of blood into the tube, which is quickly seen through the window. 3. Lastly, but by no means least, when the fluid is entering properly there is no change visible at the

point of entrance into the vein; if, however, the needle is not properly situated in the vein, and the fluid is escaping into the tissues, a swelling will be observed adjacent to the point of entrance of the needle. This is an imperative signal for the withdrawal of the needle and its insertion at another point. Usually it takes about six to eight minutes for the fluid to pass into the circulation; a flow more rapid than that is apt to cause a too sudden increase in the blood-pressure, with unhappy result.

When gas bubbles appear in the glass tube leading from the jar, we are informed that the end of the flow is at hand. A pad of sterile gauze is placed over the point of the needle, and while a little pressure is being made by one hand, the needle is rapidly withdrawn from the vein with the other, the remaining fluid still emerging from its mouth. The gauze is slightly pressed over the site of the injection, and firmly fixed in place with a snug bandage. The patient is placed in bed, and I give distinct orders that he must not leave his bed for any reason whatever for at least ten hours. I usually give the injection in the early afternoon, and the patient does not leave his bed until the temperature is normal, the next day. He then dresses and goes about his affairs as though nothing had happened to him. The patient should eat very little for at least six hours before and after the injection.

It goes without saying, that in cases in which the veins of the arm are not sufficiently prominent, a little cocain or alypin should be injected and the vein exposed. The rest of the technique is the same as just described. It is better, however, not to expose the vein if it can be avoided, as the cut leaves an embarrassing scar.

Several points must be emphasized in this connection: The saline solution must be made with fresh boiled distilled water and chemically pure sodium chlorid; the solution must be free of any particles or substances, and it must be absolutely clear; the less sodium hydrate used, the better, consequently a fresh solution should be made up every few days; the fluid should be at blood temperature when injected. If the patient shows signs of faintness or collapse, stop the injection immediately, and stimulate with caffein, camphor, strychnin and oxygen if necessary. All of these stimulants should be at hand, in readiness, as in a major operation. The injection should never be given at night, as fatal syncope or collapse might occur, and it would not be noticed by the attending nurse.

Injection of an Oily Suspension.—For the administration of salvarsan in ambulatory practice, the best method is in an oily emulsion. In the majority of cases, this injection is absolutely painless, and it has the advan-

tage of permitting the patient to obtain the treatment without any demand on his time. Kromayer (*Berliner klinische Wochenschrift*, September 2, 1910) first gave salvarsan in this form, mixed with liquid paraffin. He gave small doses of 0.1 gm., repeated every day for five or six days. He claims to have had satisfactory results.

Pollitzer (*New York Medical Journal*, March 4, 1911) describes his method of injection. He makes a forty per cent. suspension of salvarsan by mixing ten ampuls of salvarsan in fifteen c.c. of iodipin (iodized oil of sesame). One c.c. of this suspension contains 0.4 gm. of salvarsan. He injects one c.c. into the erector spinæ muscle at the level of the third or fourth lumbar vertebra. He declares that the effect of this injection is as good as that of the intramuscular or subcutaneous method.

Meltzer (*Medical Record*, March 25, 1911) advocates injecting salvarsan into the sacro-spinal muscle. He states that the pain is diminished to the minimum degree and absorption is increased to the maximum.

I have given about twenty-five of these iodipin injections and have found them to be a fairly good substitute in cases in which it is not desirable or practicable to administer the salvarsan intravenously. I use a suspension of 0.6 gm. salvarsan in five c.c. of iodipin. This suspension is thoroughly mixed in a sterile mortar, and injected into the buttocks, or sacrospinal muscles, with a Luer or Record syringe. Half of this amount is injected into each side of the body (Fig. 4). The patient goes home immediately and rarely is there much pain. One patient, to whom I have not been willing to give an intravenous injection, has already received five of these injections at intervals of two weeks, without the slightest pain or discomfort, and with remarkable benefit. Another patient complained of severe pain which first appeared on the eighth day after the injection and passed off within a day or two. Whether or not this method will prove to be as effective as the alkaline intramuscular or intravenous methods, remains to be seen, but it is extremely doubtful, owing to the large granule which forms as the result of the suspension in oil, thus making absorption more difficult.

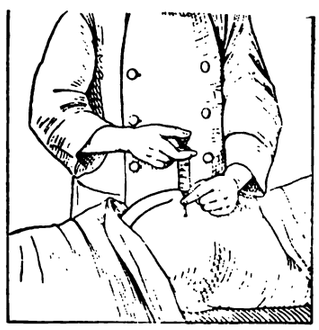


FIG. 4. Intramuscular Method.

Various other methods have been suggested, which will be mentioned briefly:

Lenzmann (*Medizinische Klinik*, February 5, 1911) sterilizes the skin of the back, and anesthetizes it with novocain. Then he injects subcutaneously 200 c.c. of an alkaline solution of salvarsan. The region is now massaged thoroughly, so that the fluid may be distributed and absorbed before the effect of the novocain passes off. Later on, the patient feels a little burning, which may cause more or less temporary pain.

Hans Leyden (*Medizinische Klinik*, December 25, 1910) cleans the skin of the inner arm or back so that it is free of fats, etc. He then prepares an alkaline solution of salvarsan, as for the intravenous injection, and rubs it thoroughly into the skin. No local anesthesia is necessary. He claims to have had excellent results with this method of skin absorption.

Isaac (cited by Ehrlich, *Deutsche medizinische Wochenschrift*, No. 52, 1910) employs an oil emulsion, injected intramuscularly. He injects 0.1 gm., once a week for six weeks, and states that this treatment has produced a negative Wassermann reaction in one hundred per cent. of his cases.

Blaschko (*Berliner klinische Wochenschrift*, No. 35, 1910) has injected a solution or emulsion of salvarsan into the evacuated intestine by means of an Oidtmann glycerin syringe, and prevented evacuation for several days by the use of opium. Absorption took place to a slight degree, and the clinical result was very slight.

THE SPIROCHETE PALLIDA

Demonstration of the Spirochetes.—Smear preparations as well as sections and fresh preparations may be used to demonstrate spirochetes. Animal experimentation may be left out of consideration, as the cultivation of spirochete pallida has not yet been successfully accomplished.[1]

Mode of Preparing the Test Material.—Chancres and papular erosions are first thoroughly cleansed by rubbing with a cotton swab, saturated with physiologic salt solution, in order to remove the superfluous secretion, which as a rule, contains only few spirochetes, but numerous other microorganisms. The lesion is then dried. When iodoform or other medication has been used, it is removed by swabbing the lesion and then covering it with pledgets of cotton saturated with physiologic salt solution. The erosion surface is then scraped with a platinum loop until the oozing of a light-coloured serum (Reizserum) is produced; the admixture with blood is avoided as far as possible.

The tissue fluid (serum) may also be obtained by making pressure like milking, on the chancre or papule, between two fingers. Von Hoffmann recommends scrapings obtained from the edge of the erosion by means of a platinum spatula, as particularly desirable material for examination. Numerous spirochetes are also found in the expressed juice of exudated primary lesions. The horny layer of healed efflorescences is removed with a knife, avoiding bleeding, and the serum obtained from the edge is used for examination. Pustules and pemphigoid blisters may also be opened and the serum taken from their base for examination.

For the Extraction of Test Material from Glands.—Von Hoffmann gives the following directions: "The skin of the inguinal region is shaved, disinfected and washed with physiologic salt solution. A syringe, sterilized

[1] Spirochetes pallida have been cultivated to a number of generations, and animal experimentation successfully conducted at the Rockefeller Institute in New York. Noguchi: Journal of Experimental Medicine, Vol. XIV, No. 2, 1911, and Jour. Am. Med. Ass'n, July 8, 1911. Noguchi has obtained the spirochete pallida in pure culture, and he considers it as established that testicular lesions produced in rabbits by means of syphilitic materials are the result of the multiplication of the pallida and not of some associated indefinite parasite. *Author's note.*

by boiling, having a capacity of about five c.c., furnished with an asbestos piston and armed with a long, thick needle, is washed within and without with sterile salt solution, and the needle is plunged into the inguinal gland, which is held fixed with the left hand. By careful manipulation, the needle is inserted into the substance (cortical layer) of one of the largest glands, in its longitudinal diameter. Aspiration is then begun, at the same time gradually withdrawing the needle from the gland. If enough serum has not been obtained, the needle, guided by the left hand, is inserted into one or more of the adjacent glands, until several drops of whitish red fluid are obtained. The movement of the punctured gland along with the needle, when moved from side to side, indicates that the needle is correctly placed in the gland substance. The gland juice thus obtained is then emptied into a sterile glass dish, provided with a cover, thoroughly stirred, and thin smears made as rapidly as possible."

Blood is obtained for examination by means of a venous puncture, or by pricking the lobe of the ear. At least one c.c. is taken and received in ten times its volume of one-half per cent. acetic acid. The dissolved blood is centrifugalized and the sediment examined.

Preparation of Stained Specimens.—Cover glasses or slides, previously immersed in a mixture of equal parts of alcohol and ether for several days and then carefully polished, are used for the preparation of stained specimens. A drop of serum obtained by irritating the erosion (Reizserum) is picked up on the edge of a cover glass; this edge is then placed on the left edge of a slide at a sharp angle pointing outward, and as soon as the serum has spread over the surface of the cover glass it is rapidly drawn over the slide. In this manner a thin, evenly spread smear is obtained. Fixing is accomplished by a ten minute immersion in absolute alcohol or by means of osmic vapour.

Fixation by osmic vapour may be done in the fixation tubes described by Hamm. The bottom of the tube is filled with glass wool, impregnated with a one-per-cent. solution of osmic acid in one-per-cent. chromic acid. The slide is placed in the tube for a minute or two, the specimen then spread over it, and while still moist it is exposed to the osmic vapour for from twenty to forty seconds; it is then dried in the air and drawn through a flame three times.

Fixation by osmic vapour may also be done according to this procedure: Place a glass dish having a diameter of five c.m., and containing five c.c. of a one-per-cent. solution of osmic acid, and ten drops of glacial acetic acid, into a larger glass dish. The slides are now laid on top of this double dish for

two minutes. The serum to be examined is spread upon that side of the slide which has been exposed to the vapour, and the slide, while still moist, is replaced in the same position to be vapourized for one or two minutes. The preparation having been allowed to dry in the air, is immersed in a very light red solution of potassium permanganate, rinsed in water, and dried between layers of blotting-paper.

Methods of Staining.—A number of methods of staining have been advocated, but thus far the best results have been obtained with the Giemsa solution, marketed by Grübler, of Leipzig, and Leitz, of Berlin.

Preparation of the Giemsa Stain.—Ten drops of Giemsa solution are mixed with ten c.c. of acid-free distilled water, by gently shaking in a beaker, care being taken that none of the dye is precipitated. The stain is to be freshly prepared each time, just before being used.

Staining.—The slide is placed, prepared side downward, upon two small glass rods, resting on the bottom of a flat glass dish, and flooded with the staining solution. The time required for staining is about one to two hours. The slide is taken out, after the film which forms on the surface of the solution has been removed with blotting-paper; it is then washed with water and dried between layers of blotting-paper.

Rapid Staining.—The smears are flooded with diluted Giemsa solution and warmed over a small flame until steam is formed; at the expiration of a quarter of a minute the stain is poured off. This procedure is repeated four times, with this difference that the stain is allowed to act a full minute the last time. This is followed by a brief washing in water and drying with blotting paper.

In a well-stained Giemsa preparation, the spirochetes appear clear red and the leukocytes, blackish red; if they appear blue the stain has not been successful. When examining for spirochete pallida, the fields containing red blood cells receive first consideration, as the parasites are usually found near them. The examination under the microscope is carried out with the oil immersion lens and strong ocular (compensation ocular, No. 4).

Examination of Fresh Specimens.—A small drop of the material is placed upon a cover-glass, a little physiologic salt solution is added, and the cover-glass is then placed upon a slide and edged with vaseline or wax. The examination may also be accomplished with the hanging drop, but the drop must necessarily be quite flat. Apochromate, with compensation ocular Nos. 6–12, may be used, but spirochetes are usually found more easily with the aid of dark field illumination.

Examination of Sections.—The older method of Levaditi has given

the best results. The sections must be no thicker than two mm. All apparatus used must be scrupulously clean.

1. Fixing in a ten-per-cent. solution of formalin for twenty-four hours or more;

2. Hardening in ninety-five per cent. alcohol for about twelve hours;

3. Washing in several changes of distilled water, until the sections sink to the bottom;

4. Impregnating with a 1.5 to three-per-cent. solution of silver nitrate, contained in a bottle with a capacity of 100 c.c., for from three to five days, in an incubator at a temperature of 35–37° C. This solution should be renewed each day;

5. Reduction with the following solution, with which the sections remaining in the bottle after the silver solution has been poured off, are flooded:

Pyrogallol	4.0	
Formalin	5.0	
Distilled water	100.0	M.

The sections are then allowed to remain forty-eight hours in this solution at ordinary room temperature. The solution must be prepared freshly as required, and renewed each day;

6. Brief washing with distilled water;

7. Hardening in increasing strengths of alcohol and imbedding in paraffin. The sections should not be thicker than 5–10μ. Counterstaining is not required.

[**Other Methods of Staining Spirochete Pallida (Spirochaetes: Bosanquet**).—Davidsohn recommends the use of cresyl violet. Oppenheimer and Sachs use carbolic gentian violet (concentrated alcoholic gentian violet solution, ten c.c., solution of phenol, five per cent., 100 c.c.). Proca and Vasilescu use Gino de Rossi's cilia stain (dissolve fifty gm. pure phenol and forty gr. tannin in 100 c.c. water and add to this 2.5 gm. basic fuchsin dissolved in 100 c.c. absolute alcohol. Stain in this for ten minutes, wash and dry. Then stain with a mixture containing concentrated alcoholic gentian violet, ten c.c.; phenol, five gm.; distilled water, 100 c.c.).

Reitmann advises that films should be first treated with a five-per-cent. solution of phosphoric acid in water for five minutes and then stained with carbol-fuchsin, warmed.

Goldhorn uses a complicated preparation of polychrome methylene blue (methylene blue, lithium carbonate and eosin), and McNeal also uses

methylene blue and eosin (crude methylene blue, twenty parts; pure medicinal methylene blue, ten parts; eosin (yellowish), twenty parts; and pure methyl alcohol, 100 parts. Stain on cover slip for forty-five to sixty seconds; wash in dilute solution of sodium carbonate (one drop of one-per-cent. solution in ten c.c. water).

A special method of staining with India ink is suggested by Burri. For this purpose, ordinary India ink is diluted with water (1 part in 6, or 1 in 10). The solution is sterilized and allowed to stand for two weeks, the supernatant fluid being then ready for use. A loopful of suspension of the organisms is mixed with a drop of the ink-solution, spread on a slide and allowed to dry. The spirochetes are then easily seen as colourless spirals on a dark background. Some writers prefer a stronger solution of the ink, i.e., 1 part in 2 of water.

Mandelbaum stained living spirochete pallida in a hanging drop by adding a loopful of Loeffler's methylene blue solution along with a loopful of decinormal soda solution. Meirowsky makes a paste of methyl-violet and salt solution, and rubs it into the previously cleaned surface of the chancre. In the serum which exudes, there are found stained specimens of spirochete pallida and spirochete refringens. Certain more deeply staining dots in the substance of the organisms he regards as nuclei. Crystal violet is as efficacious as methyl violet.—The Editor.]

Morphology.—In a well-stained Giemsa preparation, the spirochetes are shown as very fine, pronouncedly red-coloured spirals, the ends of which are mostly sharply pointed. They show six to twenty or more regular, deep, steep, corkscrewlike twists. A stretched form, presenting essentially the same picture, including the numerous windings, is also characteristic. As a rule, the spirochetes lie singly, at times they are seen in pairs, placed at a sharp angle towards each other, or in a row, or in a Y-shaped formation; occasionally they are seen in heaps, interwoven in the shape of braids or coils. In the same specimen, adjacent to typical forms, atypical forms are found, with their coils flattened for some distance, or wholly drawn out to the shape of a thread. Others have their ends coiled spirally on themselves, or exhibit bulbous swellings at their extremities. These changes are possibly due to damage sustained in the course of smearing or fixing the preparation.

Living spirochetes are characterized by their tenderness, their slight refractive power, their regular, close, deep, steep and usually numerous windings, and their constancy of form when in motion or at rest. This constancy of form lends to the spirochete a peculiarly artificial, rigid appear-

ance. The spirals, as a rule, diminish in height, as they approach the ends, the latter usually being pointed. Very long, as well as very short specimens of spirochete are found in the same preparation. The local movement of the spirochetes is very slight; rotary motion around their axis, backward and forward glidings and bending of the entire body is observed. This movement may be likened to the bending and recoil of an elastic reed.

Differential Diagnosis.—For the differential diagnosis, we must consider particularly the spirochete refringens, spirochete balanitidis, spirochete buccalis, spirochete vincenti, spirochete dentium, and spirochete pallidula pertenuis. As a rule, after some practise and with close attention, the spirochete pallida can be differentiated with certainty from these forms. An exception to this rule is the spirochete pallidula, found in framboesia tropica (yaws), from which the spirochete pallida has not, as yet, been morphologically distinguished.

In the Giemsa preparation, the spirochetes pallida appear red; most other spirochetes, on the other hand, are coloured from blue to violet. They are, in proportion to their length, usually thicker and plumper, and in their finer forms, shorter than the spirochete pallida. Their ends are usually blunt and their coils irregular and flat, in comparison with those of the spirochete pallida. In the fresh preparation, they have a more active motility, and stronger refractive properties than the spirochete pallida, and are on that account much more easily detected. Furthermore, they lack the constancy of form displayed by spirochete pallida, they show spiral windings only while in motion, and when at rest they exhibit a flatly woven form, closely approximating a straight line. A very close resemblance to the spirochete pallida is exhibited by the spirochete dentium. This also stains red with Giemsa stain, is very slender, weakly refractive and constant of form when in motion. It differs, however, from spirochete pallida in the smaller depth of its windings. However, to avoid errors in diagnosis, when it is based solely upon the morphologic peculiarities of the spirochete, only such specimens which fully conform to the normal type should be considered.

THE SERUM DIAGNOSIS OF SYPHILIS, ACCORDING TO WASSERMANN

The positive result of the Wassermann reaction indicates that the individual furnishing the examined serum is or has been infected with syphilis. The theory of the reaction is based on the observation that a combination of antigen and antibody will bind complement, whereas neither antigen nor antibody alone possesses any or a very slight affinity for complement.

A hemolytic system (red blood-cells + serum, obtained from a rabbit previously injected with red blood-corpuscles) serves as an indicator for the complement fixation. If we add a hemolytic system to a solution containing antigen + antibody and complement, hemolysis does not take place, because of the complement entering into the antigen + antibody complex, whereas hemolytic amboceptor and complement are required for the production of hemolysis. If, on the other hand, the solution contains either antigen or antibody and complement, the complement cannot be fixed, and it remains free to produce solution of the red blood-corpuscles of the added hemolytic system. The absence of hemolysis, therefore, shows a positive reaction, and its presence indicates a negative reaction.

In the examination for antibodies, which are traceable to luetic infection, blood serum is used; in parasyphilitic diseases of the central nervous system lumbar fluid is used. A specially prepared extract of the livers of congenitally syphilitic infants is used as antigen, the livers having been previously tested as to their fitness for this purpose. The method of procedure is as follows:

The liver extract is added to the previously inactivated serum, complement consisting of guinea-pig serum is then added, and the mixture is put into the incubator for one hour, to permit the action between antibody, antigen and complement to take place. On the expiration of this time, the hemolytic system is added, and the tubes are again allowed some time in the thermostat, and thereupon are set in the refrigerator overnight. The result of the test may then be determined. If the examined serum contains

antibodies, that is, if the result be POSITIVE, hemolysis *has not* taken place, the red blood-corpuscles are collected at the bottom of the tube and the supernatant liquid is colourless; in the absence of antibodies, that is, if the result is NEGATIVE, this is shown by the fact that solution *has* taken place, the tube contains no sediment of red blood-corpuscles, but the entire almost clear liquid has become red, coloured by the dissolved blood pigment.

Method of Applying the Reaction.—The blood necessary for the reaction is obtained by a venous puncture, the median basilic vein being the best for the purpose, or by the use of a cupping cup. Six to eight c.c. are taken from adults, and one and one-half to two c.c. from children. The blood is received into sterile centrifuge tubes, and after clotting, it is separated from the walls of the tube by means of a sterile needle and centrifugalized to obtain the required serum. The separated serum is decanted and immediately inactivated (complement destroyed) by heating it on a water bath to 56° C. for half an hour.

Two control sera, similarly inactivated, are always examined simultaneously with the suspected serum, one from a known syphilitic serum, rich in antibodies, and the other a known normal serum. The serum must be examined in as fresh a state as possible, as syphilitic serum which has been kept for a time may lose its property of binding complement, and vice versa; normal serum may develop this property. Two specimens of the suspected serum, namely, 0.2 c.c. and 0.1 c.c., and one each of 0.2 c.c. of the control sera, are employed.

Antigen.—If the liver furnishing the antigen is not to be used at once, it may be kept in a Morgenroth refrigerator in a frozen condition.

Preparation of the Aqueous Extract (Wassermann and G. Meyer). The liver is cut into small particles, with a knife and scissors, mixed with four parts of physiologic salt solution, to which phenol in the proportion of 0.5 per cent. is added, and the mixture agitated in the shaking apparatus for twenty-four hours. For example, 360 c.c. salt solution (0.85 per cent.), 100 gms. liver, 40 c.c. phenol, 0.5 per cent. The resulting mass is centrifugalized until a perfectly clear extract is obtained.

Alcoholic Extract.—Michaelis furnishes the following formula for its preparation: "The liver is minced in a mortar, ten volumes of absolute alcohol are immediately added, and the mixture shaken with the aid of glass beads for ten to twelve hours. At the expiration of twenty-four hours, the clear liquid is removed from the sediment with a pipette, and preserved in the refrigerator, to be used as stock solution (antigen). For each test of

the reaction, a freshly prepared dilution of the stock solution with four parts of physiologic salt solution is employed. This alcoholic stock solution forms a slightly milky emulsion with the aqueous solution. Its slight alcoholic content does not interfere with the reaction. On allowing this milky emulsion to stand, a flocculent precipitate gradually settles on the bottom; the clear supernatant liquid is then ineffective, as the active principle is fixed in the precipitate and the emulsion must be well shaken to render it active again. One c.c. of this diluted emulsion is as a rule employed for the reaction, although considerable latitude as to the quantity of liver extract is permitted."

Alcoholic extracts of normal organs, prepared in the above-described manner, have been recommended as practicable antigen. Fleischmann found four out of five extracts of normal livers available. Michaelis has used a very effective alcoholic extract of normal (human) hearts. It is better, however, at the present stage, at least, to use the extract of syphilitic livers in order to obtain unobjectionable results.

Previous to its employment, each extract must be tested as to its availability by comparison with a known syphilitic and a known normal serum, as available extracts are not always obtained, even from syphilitic fetal livers.

Antigen is considered particularly efficacious if 0.1 c.c. + 0.1 c.c. of syphilitic serum inhibits hemolysis completely. Antigens, of which 0.2 to 0.4 c.c. + 0.1 to 0.2 c.c. of luetic serum are required for complete inhibition, may also be used, provided they do not produce inhibition either with normal sera or by themselves in double amount (G. Meyer). For the preliminary test of the extract, following the suggestion of Meyer, the smallest amount of extract, which by itself will bind complement, is determined by testing with 0.2, 0.4, 0.6, 0.8 and 1.0 c.c. of antigen; and furthermore, the smallest dose which will cause complete inhibition with 0.1 c.c. of luetic serum is noted.

The extracts, when kept cool and dark, often remain serviceable for several months, but they may suddenly become ineffective; for this reason it is imperative that their efficacy be controlled at each test with a known luetic and a known normal serum. In making the test, two correspondingly different doses of the extract and the serum are used, as, for instance, 0.2 c.c. of antigen + 0.2 c.c. of serum, and 0.1 c.c. of antigen + 0.1 c.c. of serum; the amounts used depend upon the result of the preliminary examination.

Complement.—Fresh guinea-pig serum serves as complement. One c.c. of a ten-per-cent. dilution in physiologic salt solution is required. The serum may be conserved for a short time (not more than forty-eight

hours) in the ice-chamber. Guinea-pig blood may be obtained by heart puncture.

Hemolytic System.—Red blood-corpuscles (erythrocytes) of the sheep, and serum obtained from a rabbit previously treated by repeated injections of washed sheep's blood-corpuscles, constitute the hemolytic system. The sheep's blood is obtained by puncture of the jugular vein and received in salt solution. The blood-corpuscles are separated by centrifugalizing, and washed several times with physiologic salt solution. The blood-corpuscles are shaken with the salt solution in the centrifuge tube, then centrifugalized and the supernatant liquid is poured off; this is repeated several times. For the test, one c.c. of a five per cent. suspension of blood-corpuscles in physiologic salt solution is used.

The hemolytic serum keeps well for some time, if put into a dark bottle and placed in the refrigerator. For the test, one c.c. of a dilution which corresponds in solving power to a serum capable of dissolving a two and a half to threefold dose of the serum, is employed.

Its titre must be determined before instituting the reaction. For trial-tests, G. Meyer recommends one and one-half, two and three fold strengths of that dilution with which good results were obtained at the last test. In order to adapt the result of the trial-test to the conditions of the actual test, the complement, with the addition of the blood-corpuscle serum mixture and two c.c. of physiologic salt solution is placed in the incubator for one hour.

If the titre of the serum has remained unchanged, complete hemolysis will be found to have taken place in the tube containing the one and one-half dilution within half an hour, and in the tube containing the twofold dilution at the latest within one hour. The threefold dilution is as a rule completely hemolysed within two hours, but that result need not be awaited in order to proceed with the reaction.

For the Determination of the Reaction the Following Are Necessary:

1. Antigen in two doses, i.e., 0.1 and 0.2.
2. The serum to be examined, 0.5 c.c.
3. Known luetic serum, 0.4 c.c.
4. Known normal serum, 0.4 c.c.
5. Fresh guinea-pig serum (1:10 NaCl solution).
6. Five per cent. suspension of sheep's erythrocytes in physiologic salt solution.
7. Rabbit serum, hemolytic for sheep's erythrocytes.
8. Physiologic salt solution.

The test-tubes should have a capacity of at least five c.c., and are

eventually filled up to that amount with physiologic salt solution. For the purpose of avoiding with certainty any possible source of error, a row of control test-tubes are employed in addition to the tubes containing the suspected sera (tubes 1 and 2).

1. A control with a double dose of antigen, to prove that the antigen itself produces no fixation (tube 3).

2. The positive control: Antigen and known luetic serum (tube 4).

3. The negative control: Antigen and known normal serum (tube 5). The controls in tubes 3, 4, and 5 serve to demonstrate the fitness of the antigen.

4. Controls to show that the sera themselves do not fix complement (tubes 6, 7, and 8).

5. A tube containing NaCl solution, complement and blood-corpuscles is employed to prove that the complement itself possesses no hemolytic properties (tube 9).

6. Control of the hemolytic system (tube 10).

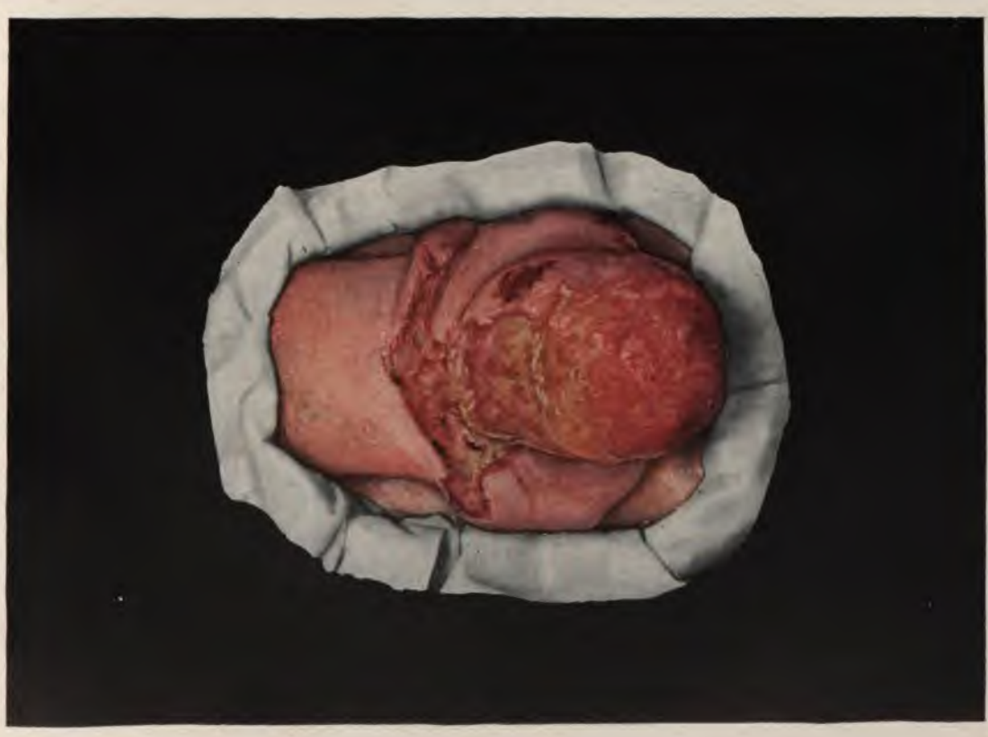
7. A tube containing salt solution and red blood-corpuscles in NaCl solution (tube 11).

In making the test, the tubes containing serum, antigen, and complement are placed in the incubator for one hour to produce fixation of the complement. Thereupon the sheep erythrocytes and the hemolytic serum, both of which have previously been kept for about one-quarter to one-half an hour at a temperature of 37° C., are added to each tube. The course of the reaction must now be watched carefully; as soon as hemolysis is complete in the control-tubes, the test-tubes are taken from the thermostat and placed on ice for twenty hours.

The determination of the reaction with an antigen, the efficient dose of which has been determined as 0.1 c.c., and giving a positive result, is illustrated by the following table:

Tube No.	Serum.				Complement.	Salt Solution.	5% Suspension of Blood-Corpuscles.	Hemolytic Serum.	Result.
	Antigen.	To Be Examined.	Known Positive.	Known Normal.					
I.....	0.2	0.2	....	....	1.0	1.6	1.0	1.0	Fixation.
II.....	0.1	0.1	....	....	1.0	1.8	1.0	1.0	"
III.....	0.4	....	....	....	1.0	1.6	1.0	1.0	Hemolysis.
IV.....	0.2	....	0.2	....	1.0	1.6	1.0	1.0	Fixation.
V.....	0.2	....	....	0.2	1.0	1.6	1.0	1.0	Hemolysis.
VI.....	....	0.2	....	....	1.0	1.8	1.0	1.0	"
VII.....	....	....	0.2	....	1.0	1.8	1.0	1.0	"
VIII.....	....	....	....	0.2	1.0	1.8	1.0	1.0	"
IX.....	....	....	....	....	1.0	3.0	1.0	....	No hemolysis.
X.....	....	....	....	....	1.0	2.0	1.0	1.0	Hemolysis.
XI.....	....	....	....	....	....	4.0	1.0	....	No hemolysis.

The same, Ten Days after the Injection



Unctuous Erosive Chancre, Three Months Duration

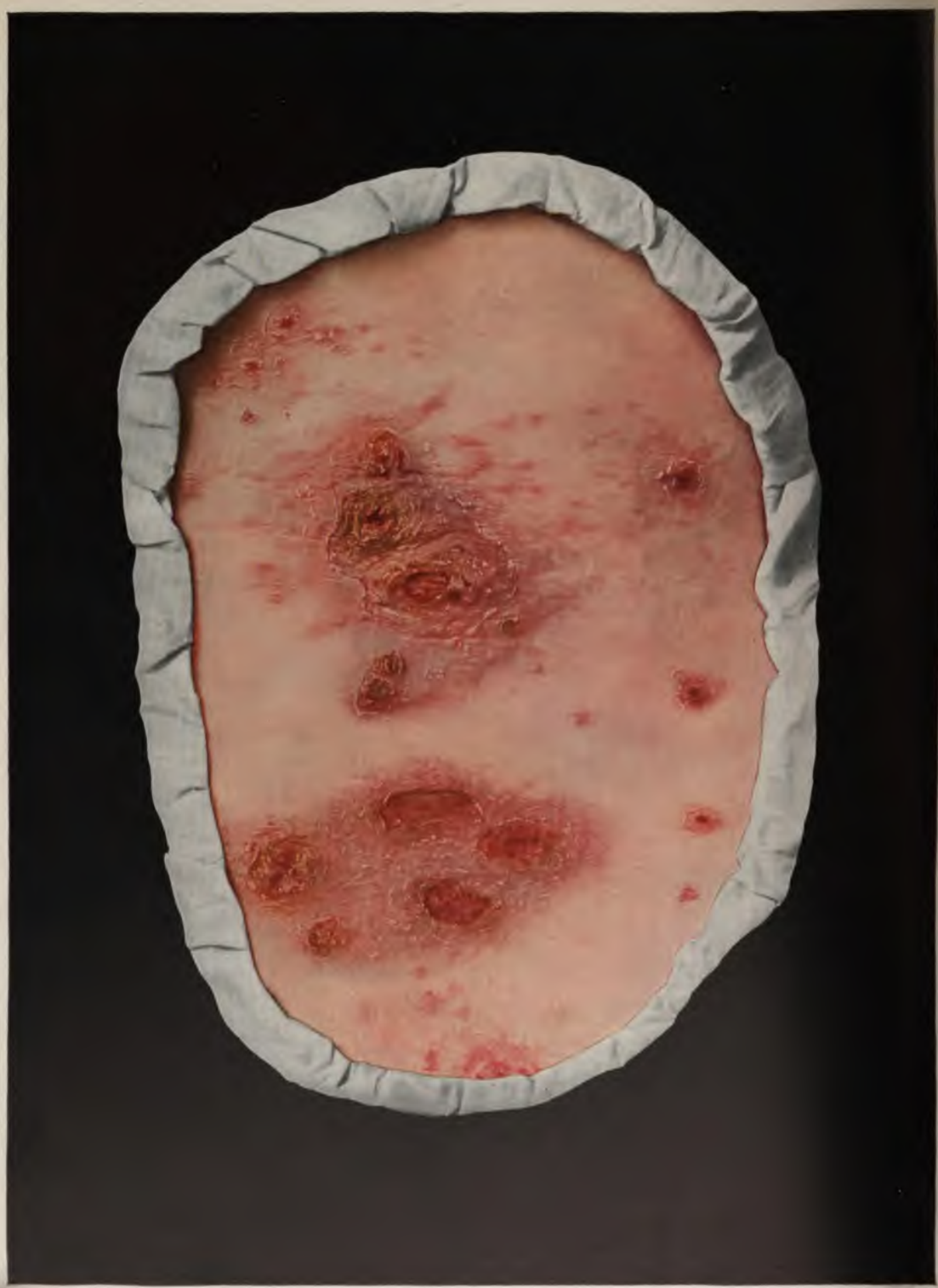
The same, Ten Days after the Injection

Ulcerating Syphilide

Rebman Company, New York

The same, Eight Days after the Injection

Ulcerating Syphilide

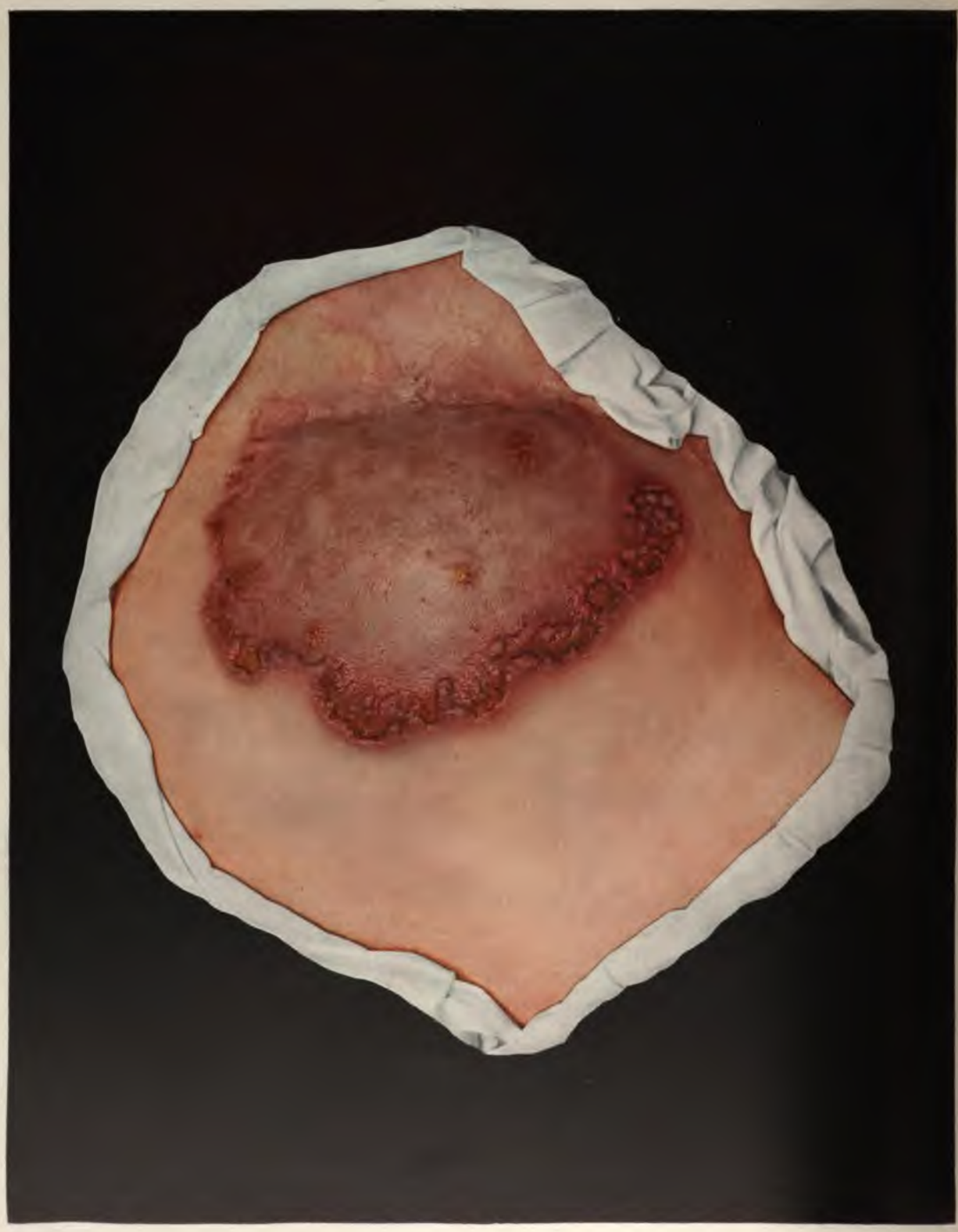


Malignant Ulcerating Eczematoid Syphilide

bman Company, New York

The same, Nine Days after the Injection

Rebman Company, New York



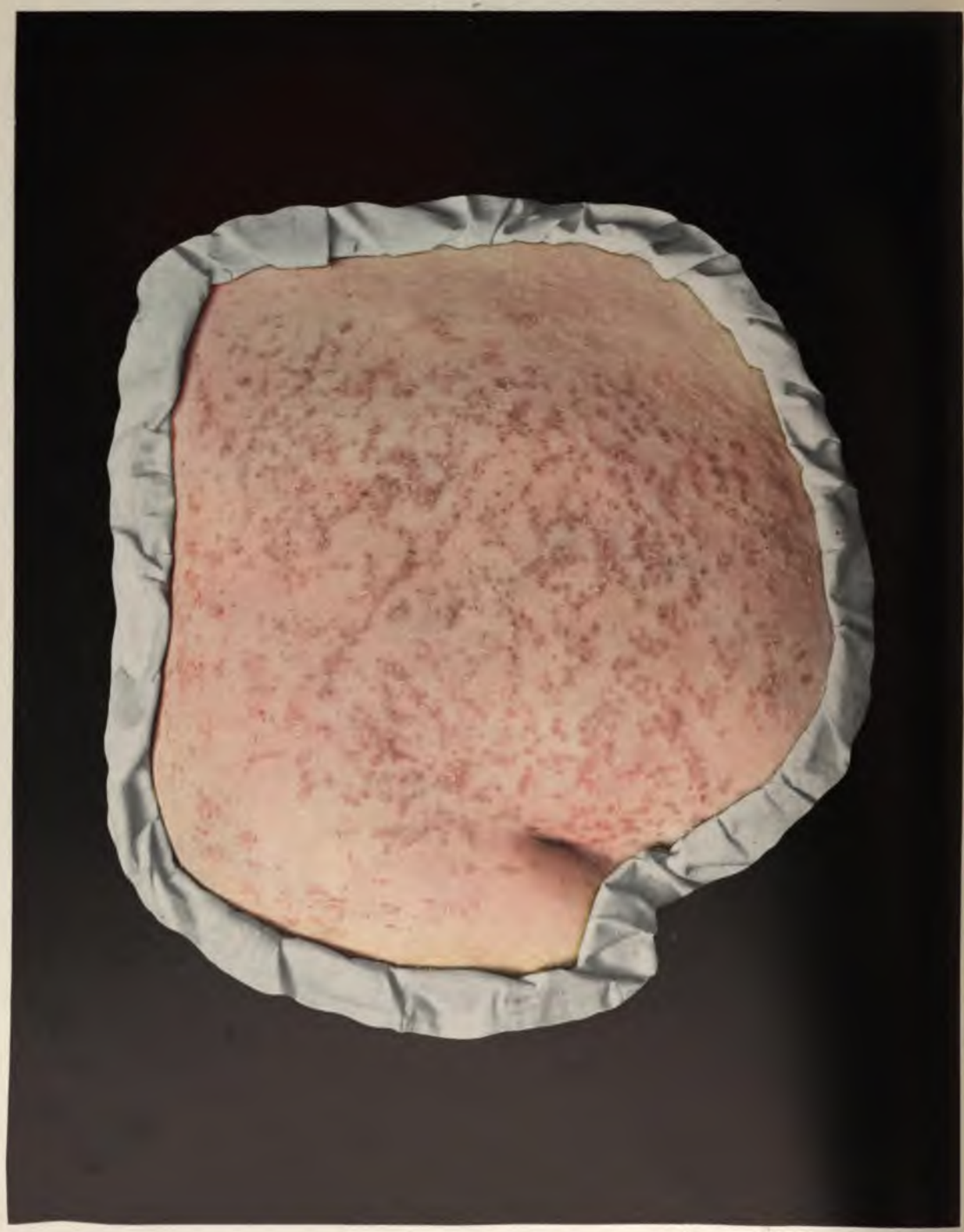
Gummatous Ulceration

(For history of the case, see text, pages 23 and 24)

nan Company, New York

The same, Ten Days after the Injection
(For history of the case, see text, pages 23 and 24)

Rebman Company, New York



Lichenoid Syphilide

(For history of the case, see text, page 28)

nan Company, New York

The same, Ten Days after the Injection
(For history of the case, see text, page 28)

Rebman Company, New York

Papulo-pemphigoid Syphilide in a Nursing Infant The same, Fourteen Days after the Injection

(For history of the case, see text, page 20)

Rebman Company, New York

Ehrlich-Hata "No. 606"

Papulo-crustaceou

Rebman Company, New York

The same, Twelve Days after the Injection

Papular Syphilide

Rebman Company, New York

The same, Eleven Days after the Injection

Extensive Rupia, Oyster-shell Shape

Rebman Company, New York

The same, Eight Days after the Injection

Severe Papular Syphilide in an Infant: Coryza: Syphilitic Infiltration of the Lip

Rebman Company, New York

Hypersensitiveness of the Seat of Injection:
Slight Necrosis at the Site of Puncture: Arsenic-Herpetic Vesicle:
Morbillous Drug Rash

Rebman Company, New York

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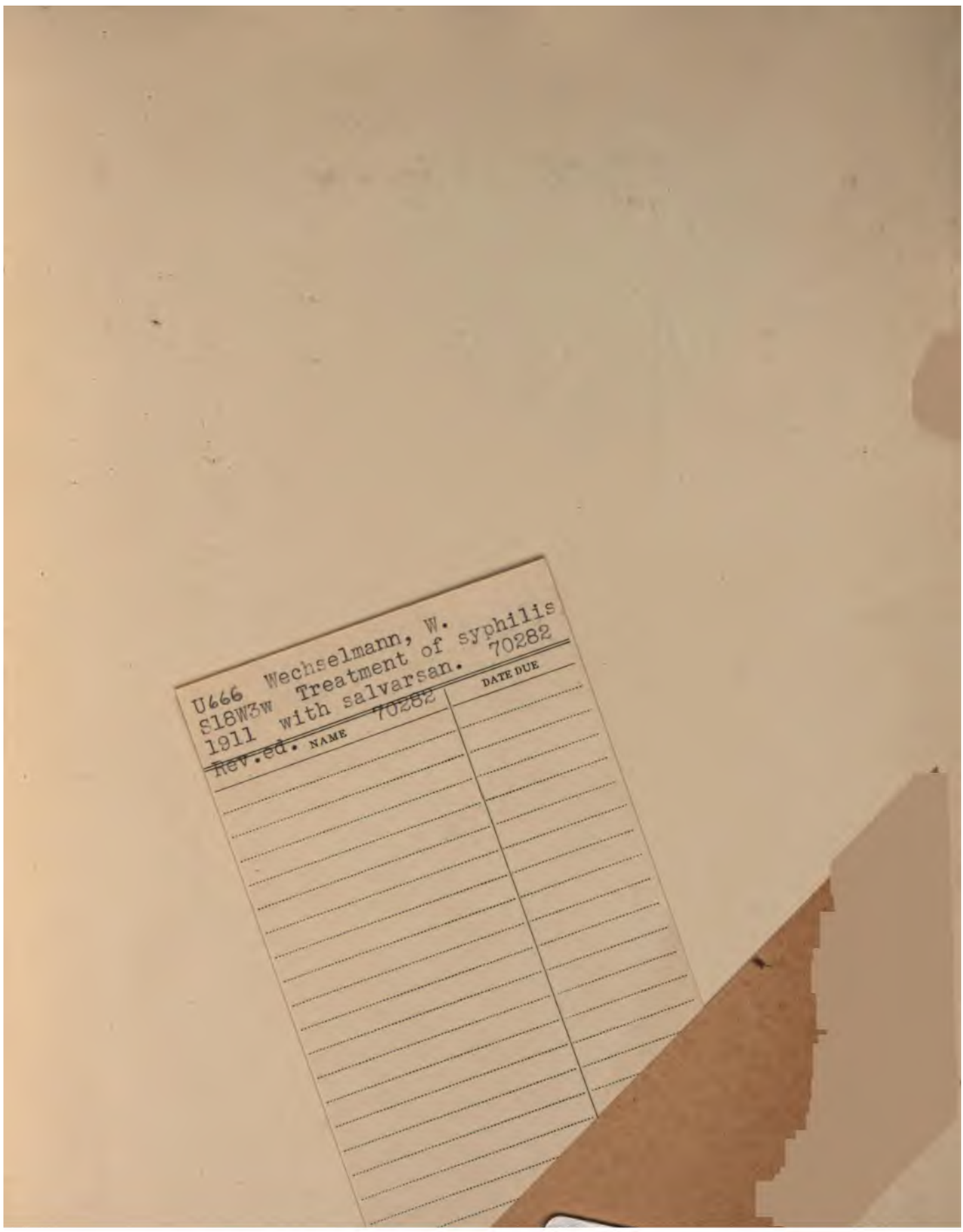
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